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OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

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Seminar on Calcium Channel Blockers—Part II

Eugene Braunwald, MD, FACC, Guest Editor

Left Ventricular Function in Mitral Valve Prolapse

Two Dimensional Echocardiography in Left Ventricular Thrombus

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A YORKE MEDICAL JOURNAL

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ANSWERS ABOUT ALDOMET® (METHYLDOPA|MSD)

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

Cardiac output and blood pressure normally increase with increasing physical activity. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[1,2]

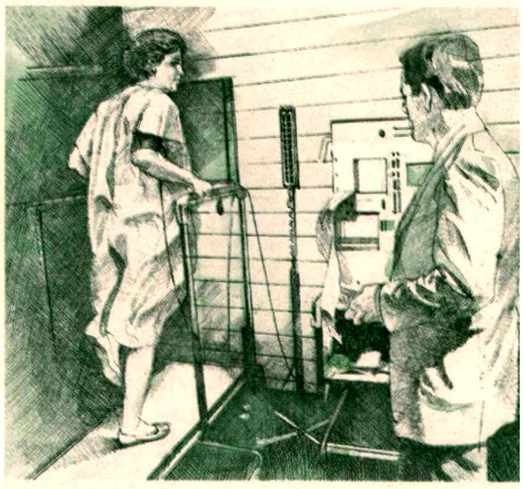
In a recent study of hypertensive patients whose cardiovascular response to exercise was evaluated before and during methyldopa therapy, "...methyldopa significantly reduced the rise in systolic pressure during the build-up ($P<0.01$) and subjective maximal stages ($P<0.05$) as well as at all phases of recovery ($P<0.01$)." Moreover, "The total duration of exercise (an index of work capacity) was unchanged with...methyldopa."[3]

Such findings can be of importance to active hypertensive patients such as the athletic individual or the person whose work requires substantial physical effort. For these and many other hypertensive patients, ALDOMET represents a logical therapeutic choice.

- With ALDOMET, exercise hypotension rarely occurs.
- Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased.
- Headache, asthenia, or weakness may be noted as early and transient symptoms.

ALDOMET® offers many (METHYLDOPA|MSD) other important features:

- Highly effective in all degrees of hypertension.
- Existing cardiac output is usually maintained.
- Renal blood flow is usually maintained.
- Has documented long-term efficacy.
- Significant adverse effects have been infrequent and the agent is usually well tolerated.



ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if prev methyldopa therapy has been associated with li disorders. It is important to recognize that a posi Coombs test, hemolytic anemia, and liver disor may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disord could lead to potentially fatal complications unl properly recognized and managed.

1. Yasky J, Carosella C, Costa O: Diagnosis of arterial hype tension by means of a graduated ergometric test, in Zanche (ed): ALDOMET® (Methyldopa | MSD) in Worldwide Clir Experience, West Point, PA, Merck Sharp & Dohme, 197 pp 56-63.
2. Mancia G, Ferrari A, Gregorini G, et al: Effects of treat with methyldopa on basal hemodynamics and on neural ci latory control, in Zanchetti A (ed): ALDOMET® (Methyld MSD) in Worldwide Clinical Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 27-39.
3. Lee WR, Fox LM, Slotkoff LM: Effects of antihypertensi therapy on cardiovascular response to exercise. Am J Card 44:325-328, 1979.

For hypertension—

ALDOMET® The most prescribed nondiuretic antihypertensive in the U.S. to
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For a brief summary of prescribing information, please see following page.
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For hypertension—

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The most prescribed nondiuretic antihypertensive in the U.S. today

ıtraindications: Active hepatic disease, such as te hepatitis and active cirrhosis; if previous thyldopa therapy has been associated with liver ɔrders (see Warnings); hypersensitivity.

rnings: It is important to recognize that a ıitive Coombs test, hemolytic anemia, and liver ɔrders may occur with methyldopa therapy. The e occurrences of hemolytic anemia or liver ɔrders could lead to potentially fatal complica- ns unless properly recognized and managed. ad this section carefully to understand these ıctions.

h prolonged methyldopa therapy, 10% to 20% of tients develop a positive direct Coombs test, ually between 6 and 12 months of therapy. Lowest ɔlence is at daily dosage of 1 g or less. This on casions may be associated with hemolytic h could lead to potentially fatal compli- predict which patients with a Coombs test may develop hemolytic . Prior existence or development of a positive ect Coombs test is not in itself a contraindication to of methyldopa. If a positive Coombs test velops during methyldopa therapy, determine ether hemolytic anemia exists and whether the itive Coombs test may be a problem. For ımple, in addition to a positive direct Coombs test e is less often a positive indirect Coombs test ich may interfere with cross matching of blood.

he start of methyldopa therapy, it is desirable to do lood count (hematocrit, hemoglobin, or red cell unt) for a baseline or to establish whether there is nia. Periodic blood counts should be done g therapy to detect hemolytic anemia. It may be ıl to do a direct Coombs test before therapy and 6 and 12 months after the start of therapy. If ombs-positive hemolytic anemia occurs, the use may be methyldopa and the drug should be ɔntinued. Usually the anemia remits promptly. If t, corticosteroids may be given and other causes anemia should be considered. If the hemolytic emia is related to methyldopa, the drug should not reinstituted. When methyldopa causes Coombs sitivity alone or with hemolytic anemia, the red cell usually coated with gamma globulin of the IgG ammaG) class only. The positive Coombs test may t revert to normal until weeks to months after ethyldopa is stopped.

ıould the need for transfusion arise in a patient ɔeiving methyldopa, both a direct and an indirect ombs test should be performed on his blood. In absence of hemolytic anemia, usually only the ect Coombs test will be positive. A positive direct ombs test alone will not interfere with typing or ɔss matching. If the indirect Coombs test is also sitive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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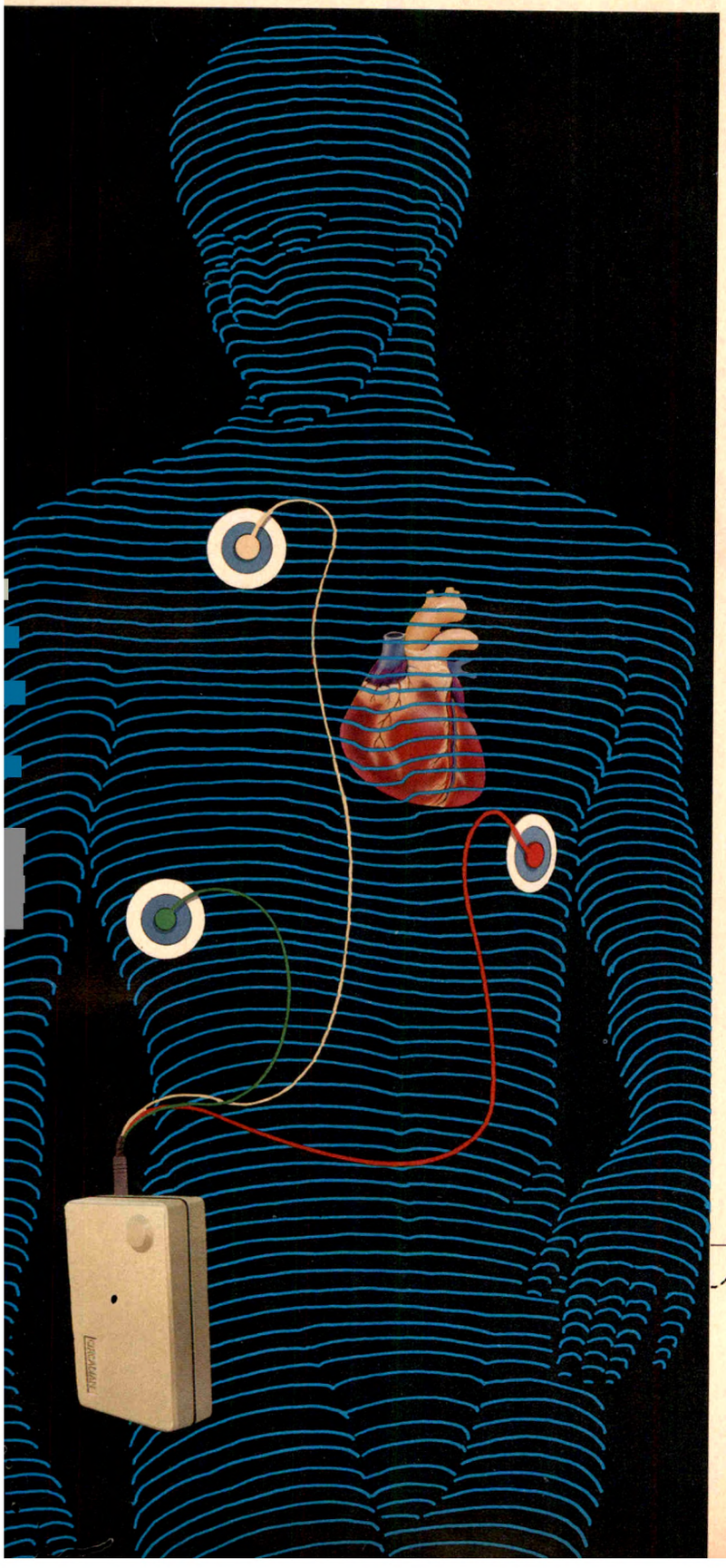

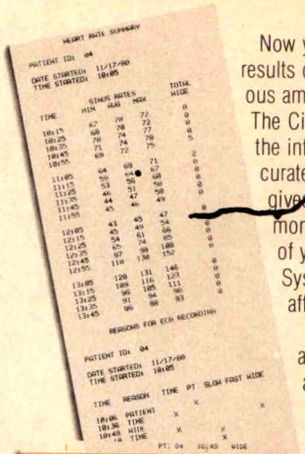

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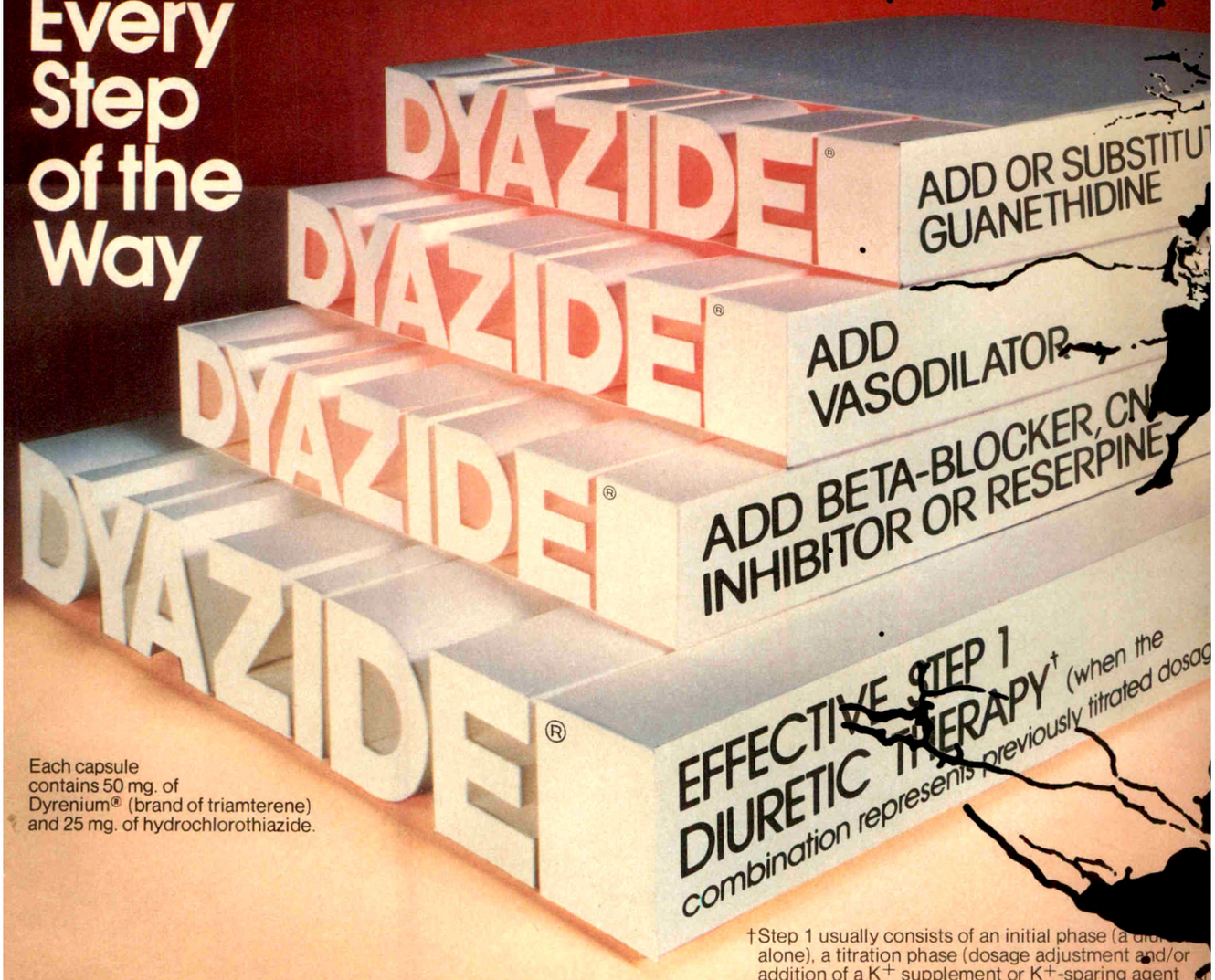

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diu alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent a maintenance phase (a diuretic alone or in combinatio with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes wi fluorescent measurement of quinidine. Hyp kalemia, although uncommon, has been repo Corrective measures should be instituted cautiousl and serum potassium levels determined. Disc tinue corrective measures and 'Dyazide' sh laboratory values reveal elevated serum potass Chloride deficit may occur as well as dilut hyponatremia. Serum PBI levels may decrease w out signs of thyroid disturbance. Calcium excretio is decreased by thiazides. 'Dyazide' should be with drawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

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INDICATIONS—Based on a review of this drug by the National Academy of Sciences National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension. Persantine tablets, 25 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. The incidence of sensitivity is generally low, but frequently seen in patients with aspirin hypersensitivity.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day taken at least one hour before meals. In some cases, higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

Tablets of 25 mg, 50 mg and 75 mg

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Please see brief summary of prescribing information on adjoining page.

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26790 A

Give your patients the KLORVESS® sparkle

Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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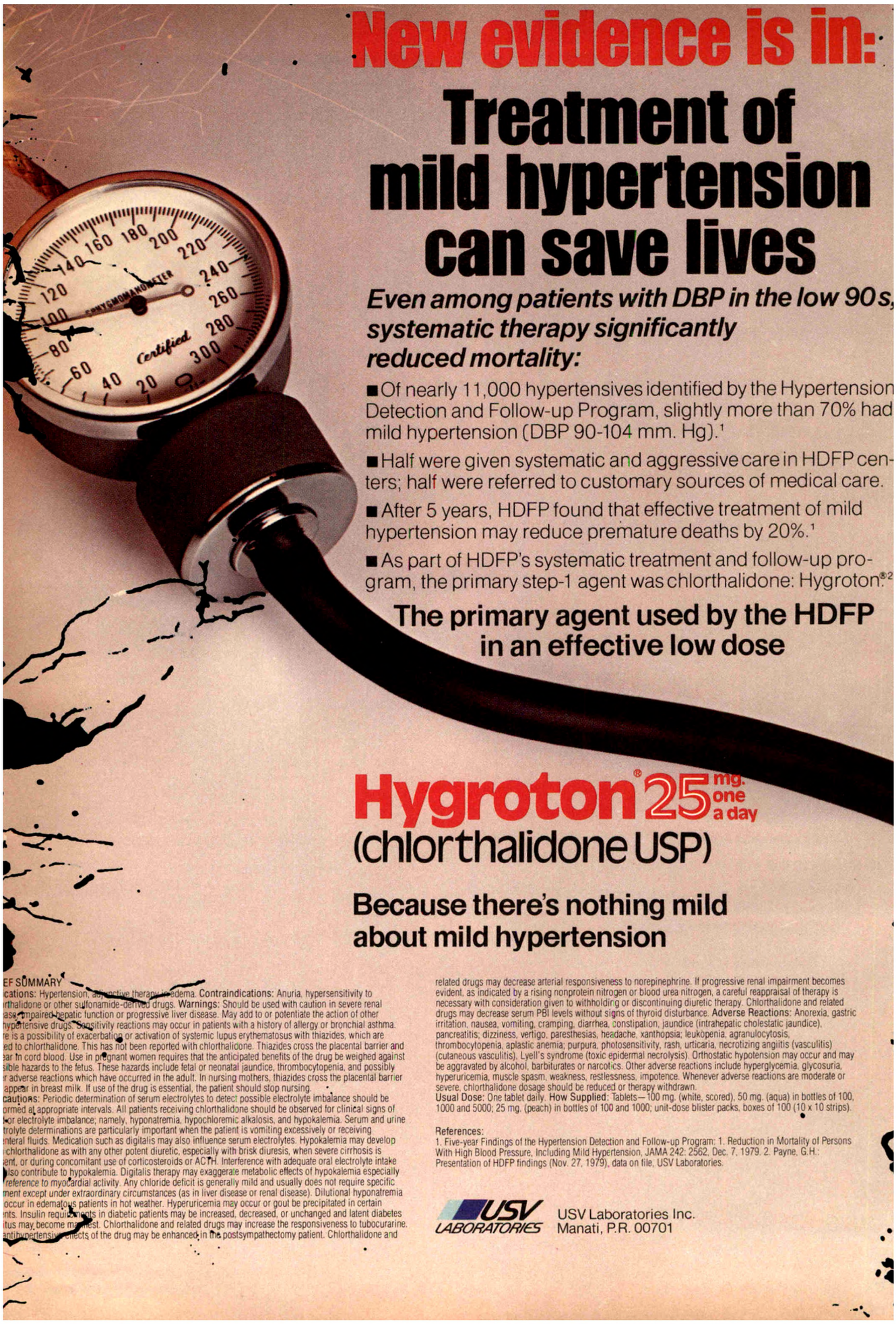

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EF SUMMARY
cations: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to rthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal ase, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other hypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. re is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are ed to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and ear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against sible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly r adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be ormed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine trolyte determinations are particularly important when the patient is vomiting excessively or receiving nteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is ent, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake lso contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific ment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain nts. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes tus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.
Usual Dose: One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:
1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H.: Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

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CLINICAL STUDIES

1 **Gated Cardiac Blood Pool Imaging and Thallium-201 Myocardial Scintigraphy for Detection of Remote Myocardial Infarction**

ALAN J. TIEFENBRUNN, DANIEL R. BIELLO, EDWARD M. GELTMAN, BURTON E. SOBEL, BARRY A. SIEGEL and ROBERT ROBERTS

This prospective study of 32 patients in whom infarct size was estimated enzymatically at the time of the acute episode and in 10 patients without infarction revealed thallium-201 imaging and radionuclide ventriculography are sensitive, noninvasive techniques for identifying prior myocardial infarction. They are particularly helpful in patients with conduction abnormalities or equivocal electrocardiographic findings. The sites of perfusion defects and of wall motion abnormalities corresponded closely and were concordant with electrocardiographic localization. Scintigraphically detectable perfusion defects persist for at least 6 months and, presumably, indefinitely. Radionuclide ventriculography also provides additional information characterizing late left ventricular function.

7 **Left Ventricular Function in Mitral Valve Prolapse: Assessment With Radionuclide Cineangiography**

JOHN S. GOTTDIENER, JEFFREY S. BORER, STEPHEN L. BACHARACH, MICHAEL V. GREEN and STEPHEN E. EPSTEIN

Radionuclide cineangiography in 47 patients with mitral valve prolapse at rest and during exercise identified a small subgroup without mitral regurgitation in whom diminished left ventricular functional reserve, manifested by an abnormal ejection fraction response to exercise, suggested a cardiomyopathic process. No patient in this series showed regional left ventricular dysfunction. The absence of these abnormalities on radionuclide cineangiography excludes with high probability the presence of coexisting significant coronary artery disease. Chest pain, arrhythmia and the pattern or degree of mitral valve prolapse on echocardiography were not independently associated with impaired left ventricular functional reserve.

14 **Cardiac Function During Rest and Exercise in Patients With Mitral Valve Prolapse. Role of Radionuclear Angiography**

GLENN E. NEWMAN, RAYMOND J. GIBBONS and ROBERT H. JONES

Assessment of ventricular function during rest and exercise in 12 patients with angiographically documented mitral valve prolapse and normal coronary anatomy, in 11 patients with normal coronary anatomy and no mitral valve prolapse, and in 11 additional patients with echocardiographically demonstrated mitral valve prolapse showed increased ejection fraction and no wall motion abnormalities during exercise. A decreased ejection fraction and wall motion abnormalities during exercise were found in 6 of 11 patients with mitral valve prolapse and angiographically demonstrated coronary arterial stenosis. These results suggest exercise-induced abnormalities in ventricular function are related to the presence and severity of coronary artery disease and not to mitral valve prolapse. Consequently, changes in ventricular function from rest to exercise assessed with radionuclide cineangiography can distinguish patients with mitral valve prolapse alone from those with prolapse and coronary artery disease.

continued on page A17

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Intended Uses—Ventricular pacing using an implantable ventricular pulse generator and lead system are for long-term therapeutic control of heart rate in patients with impulse formation or conduction disorders leading to bradyarrhythmias, tachyarrhythmias and heart block (see product labeling for detailed list of intended uses). An atrial pulse generator is for long-term therapeutic control of heart rate in patients with impulse formation disorders but with intact, functioning A-V conduction systems.

Contraindications—There are no known contraindications to the use of pacing as a therapeutic modality for the control of heart rate in patients with normal conduction systems. In certain patients with anomalies of the conduction system (WPW syndrome and related conditions), patients may be benefited or harmed by cardiac pacing. Therefore, electrophysiologic studies are required prior to therapeutic application of pacing. In addition, the patient's age and medical condition may dictate the particular pacing system and implantation procedure used by the physician.

Warnings—Diathermy should not be used on patients with pacemakers because of possible heat damage to electronic components. Electrosurgical units should never be used in the vicinity of unipolar pulse generators or bipolar pulse generators implanted in the unipolar mode because of danger of introducing fibrillatory currents into the heart via the implanted pulse generator/lead. Pulse generators may be damaged by defibrillatory discharges if the paddles are placed over the implanted pulse generator. (See product labeling for a complete list of warnings and precautions.)

Precautions—The physician should be aware that all pulse generators will ultimately cease to function due to cell depletion and may fail at any time due to random component or battery failures which cannot be predicted prior to failure. Also, that the pacing system may cease to function at any time due to lead-related problems such as displacement, fibrotic tissue formation, elevated thresholds and perforations, and that proper operation may be affected by electrical interference from certain electrical equipment.

Side Effects—Body rejection phenomena, including local tissue reaction, muscle and nerve stimulation, infection, erosion of pulse generator/lead through skin, transvenous lead-related thrombosis, embolism and cardiac tamponade.

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Intended Use—The Medtronic® Model 9700 and 9701 Programmers are designed to be used by a physician for noninvasively programming the Medtronic® pulse generators listed in their respective technical manuals. The programmers may also be used to measure the rate and pulse width of implanted pacemakers.

There are no known contraindications or major potential complications associated with use of the programmer. However, these devices should not be used without prior study of the technical manual supplied with each programmer.

Warnings—The programmers should only be used for programming the Medtronic® pulse generators designated in the respective technical manuals. Direct stimulation by energy coupling may occur if the programmers are used on other implanted devices. The programmers are not compatible with pulse generators of other manufacturers. See product labeling for a complete list of warnings and precautions.

(spironolactone)

WARNING

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see Warnings). Aldactone should be used only in those conditions described under Indications. Unnecessary use of this drug should be avoided.

Indications: *Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.*

Contraindications: *Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.*

Warnings: *Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.*

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: *Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.*

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: *Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.*

Dosage and Administration

For primary hyperaldosteronism: *400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.*

For edema in adults: *Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.*

For edema in children: *Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.*

For essential hypertension: *Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.*

For hypokalemia: *25 to 100 mg. daily in divided doses.*

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☑ *Unlike other potassium-sparers, Aldactone specifically antagonizes aldosterone, thereby mitigating secondary volume buildup.*

For these reasons, Aldactone is a valuable adjunct in the treatment of CHF.

Limitations to Consider: *Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus, Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and* Warnings *section of Aldactone prescribing information.)*

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the preceding page.

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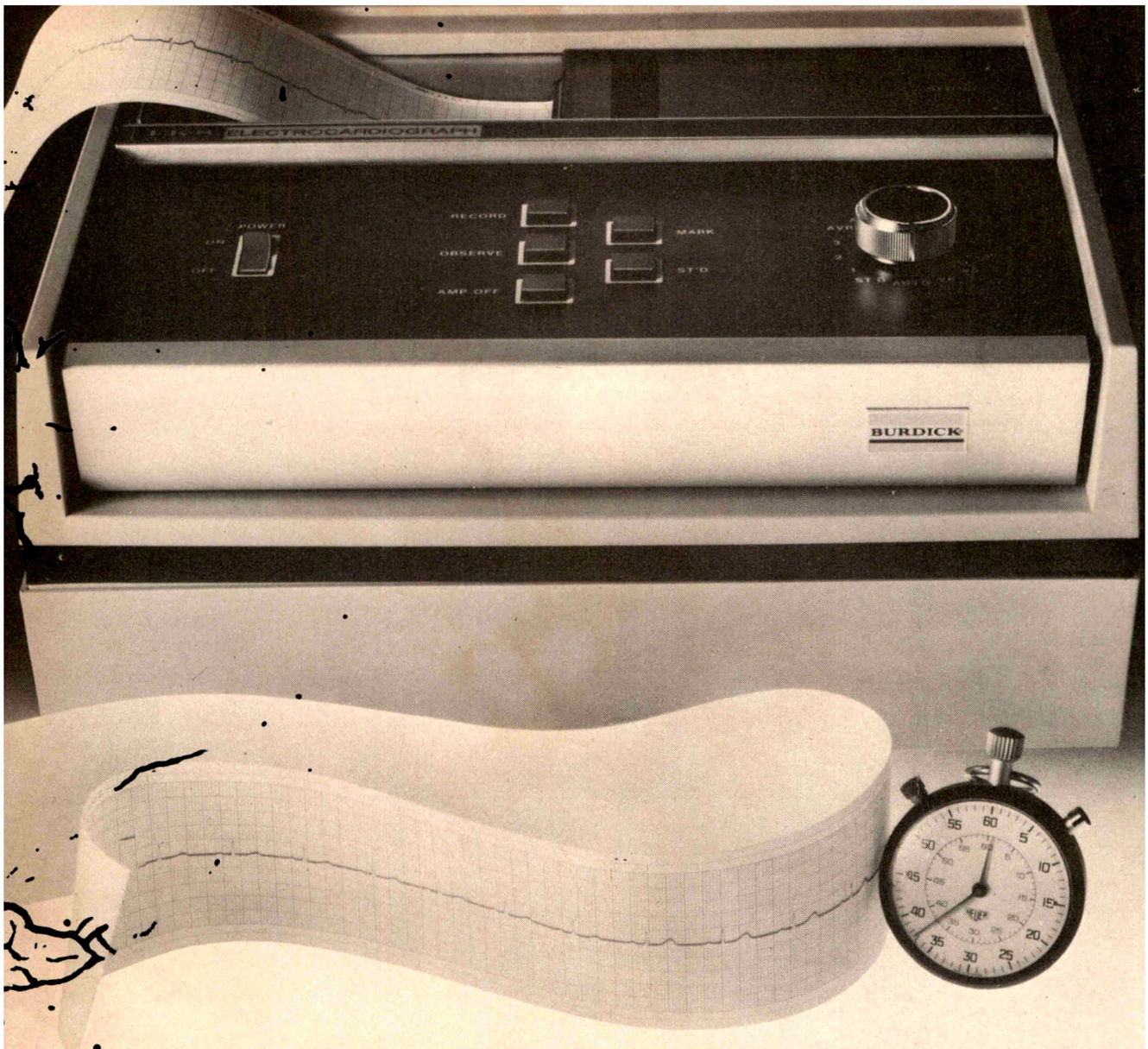

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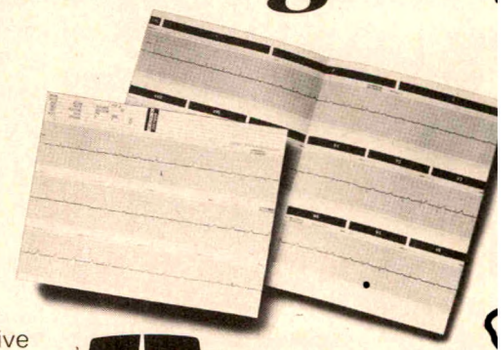

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20 Exercise Cross-Sectional Echocardiographic Diagnosis of Coronary Artery Disease

JOEL MORGANROTH, CHIN C. CHEN, DANIEL DAVID, HENRY S. SAWIN, MASAHITO NAITO, CONNIE PARROTTO and LINDA MEIXELL

Wide angle cross-sectional echocardiography in 55 patients undergoing diagnostic coronary arteriography show that new regional wall motion abnormalities during exercise represent a specific finding for the presence of coronary artery disease. Such studies were adequate for analysis in 43 (78 percent) of the 55 subjects. Normal regional wall motion during exercise did not exclude the presence of important anatomic coronary artery disease. About 50 percent of the patients with normal regional wall motion during exercise had important anatomic coronary artery disease and half of these had abnormal S-T segment depression during exercise testing. For this group, the electrocardiographic manifestation of ischemia proved more sensitive in predicting the presence of anatomic coronary artery disease than did the presence of new regional wall motion abnormalities on two dimensional echocardiography during exercise.

27 Importance of Coronary Collateral Circulation in Interpreting Exercise Test Results

JULIO F. TUBAU, BERNARD R. CHAITMAN, MARTIAL G. BOURASSA, JACQUES LESPÉRANCE and GEORGES DUPRAS

Examining the hypothesis that coronary collateral circulation can cause false negative exercise electrocardiograms and myocardial scintigrams, this study of 37 patients with 90 percent or greater isolated stenosis of the luminal diameter in one major coronary artery and no other arterial stenosis of 50 percent or greater concludes that large intercoronary collateral vessels are a common cause of false negative scintigrams rather than of false negative exercise electrocardiograms, which are largely unaffected by the degree of collateralization. Large collateral vessels may limit the quantity and location of myocardial ischemia. Exercise electrocardiography and thallium-201 scintigraphy may detect different aspects of ischemia.

33 Lack of Correlation Between Exercise Capacity and Index of Resting Left Ventricular Performance in Heart Failure

JOSEPH A. FRANCIOSA, MARY PARK and T. BARRY LEVINE

Treadmill exercise performed in 21 patients with heart failure caused by cardiomyopathy indicated that measures of left ventricular performance obtained at rest do not accurately reflect exercise tolerance and symptomatic status of patients with congestive heart failure. Exercise duration averaged 9.1 ± 7 minutes (normal value 12 or more minutes) and did not correlate with resting ejection fraction of 26.4 ± 2.7 percent. Left ventricular diastolic dimensions of 6.6 ± 0.2 cm determined with M mode echocardiography, mean velocity of circumferential fiber shortening and ratio of preejection period to left ventricular ejection time did not correlate with treadmill time. It is quite likely that hemodynamic responses and change in ventricular performance during exercise are major determinants of exercise capacity in patients with heart failure.

40 Systolic and Diastolic Properties of the Human Left Ventricle During Valve Replacement for Chronic Mitral Regurgitation

CALVIN Y. H. WONG and HENRY M. SPOTNITZ

Using M mode and two dimensional echocardiography and intraoperative measures of hemodynamic function, ventricular compliance and systolic mechanics in nine patients during valve replacement for chronic mitral regurgitation, these investigators detected large decreases in early postoperative shortening fraction. Elimination of the low impedance left atrial pathway by valve replacement was associated with a significant increase in wall stress that appears responsible for the decreased ejection fraction postoperatively. Other data emphasize the unreliability of preoperative ejection fraction as an index of cardiac reserve in patients with chronic mitral regurgitation and suggest the need for improved methods of evaluating patients with this condition as candidates for surgery. Conventional analysis of ejection fraction preoperatively underestimates the degree of left ventricular dysfunction.

continued on page A23 •

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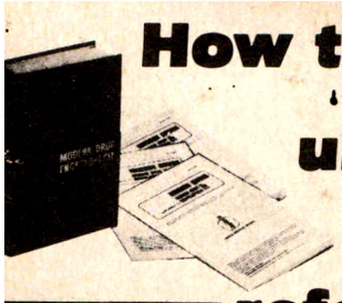

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51 Right Ventricular Performance in Mitral Stenosis

EDMUND WROBLEWSKI, FRANK JAMES, JAMES F. SPANN and ALFRED A. BOVE

Assessing right ventricular performance from computer-analyzed biplane right ventriculograms in seven normal subjects and in eight patients with mitral stenosis, these investigators found patients with mitral stenosis had elevated systolic right ventricular pressure (57 ± 6 mm Hg) but normal right ventricular end-diastolic pressure (81 ± 9 ml/m^2) and ejection fraction (0.58 ± 0.04). Left ventricular function as measured by the ejection fraction was reduced in the patients with mitral stenosis. The contractile performance of the right ventricle in patients with mitral stenosis remains normal with moderate pressure overload when there is no clinical evidence of right ventricular failure. The normal function of the right ventricle is probably maintained by hypertrophy when the pressure overload is not extreme. The cause of the reduced left ventricular function in mitral stenosis is unclear.

56 Right Ventricular Function in Adult Atrial Septal Defect. Preoperative and Postoperative Assessment and Clinical Implications

RICHARD R. LIBERTHSON, CHARLES A. BOUCHER, H. WILLIAM STRAUSS, ROBERT E. DINSMORE, KENNETH A. McKUSICK and GERALD M. POHOST

This study of right ventricular function in 20 adults with an atrial septal defect illustrates the close correlation between right ventricular function and clinical course preoperatively and postoperatively in these patients. Nuclear imaging proved beneficial in such assessments. Preoperatively, the right ventricle was dilated in all 20 patients; right ventricular wall motion was normal in 9 who were asymptomatic and had normal sinus rhythm. These and other data demonstrate severe preoperative right ventricular hypocontractibility and indicate that postoperative right ventricular size and function improve but do not necessarily become normal. These observations support early prophylactic closure of atrial septal defect and favor surgical repair even in adult patients with abnormal preoperative right ventricular wall motion.

EXPERIMENTAL STUDIES

61 Acute Effects of Ethanol on Myocardial Blood Flow in the Nonischemic and Ischemic Heart

HOWARD S. FRIEDMAN with the technical assistance of CHARLES NEAL, ANDREW DOWD, EILEEN TAYLOR and EDWARD SHAUGHNESSY

Coronary blood flow, measured with radionuclide-tagged microspheres in the anesthetized dog before and after intravenous administration of 1.7 g/kg body weight of ethanol, increased in the nonischemic myocardium. In the acutely ischemic heart ethanol produced an unfavorable redistribution of myocardial blood flow with flow in the nonischemic myocardium increasing in part at the expense of blood flow to the ischemic myocardium. The increment of blood flow appeared greatest in the subendocardial nonischemic zone whereas the decrease in flow was greatest in the subepicardial ischemic zone. This study suggests that ethanol ingestion should be limited in patients with coronary heart disease because of its "coronary steal" effect, which increases the flow in the nonischemic areas at the expense of the blood flow to the ischemic myocardium.

METHODS

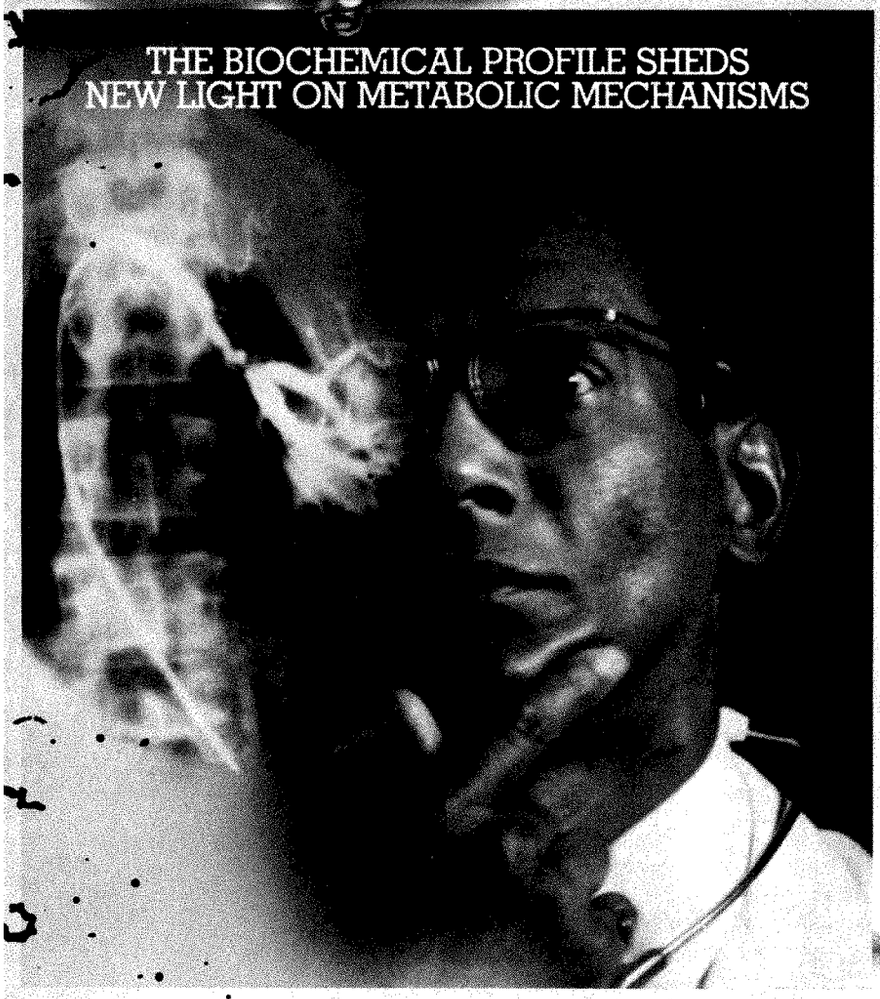
68 Derivation of Systolic Time Intervals From Doppler Measurement of Temporal Arterial Blood Flow

JAMES A. ROTHENDLER, EDGAR C. SCHICK, Jr. and THOMAS J. RYAN

Attention is drawn to a new method for recording systolic time intervals during exercise that utilizes the blood velocity profile of the superificial temporal centers measured by Doppler ultrasound. Doppler-derived left ventricular ejection time and preejection period showed excellent correlation with the conventional carotid pulse method and little intra- or interobserver variability. This method reduced motion artifact, permitted satisfactory tracings in 8 of 10 subjects who exercised through stage III of the Bruce treadmill protocol, and has potential value for use of the additional information inherent in the velocity profile.

continued on page A28

"PROFILING" TODAY'S HYPERTENSIVE PATIENT



THE BIOCHEMICAL PROFILE SHEDS NEW LIGHT ON METABOLIC MECHANISMS

While hypertension still remains an enigma, its metabolic pathways have become clearer in the past twenty years. One of the most important pathways involves the renin-angiotensin-aldosterone system. The kidney is known to secrete renin under three circumstances: 1) when the organ itself becomes ischemic; 2) when the body's sodium content is depressed; 3) when blood volume is reduced. Renin then catalyzes the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II. Besides being the most potent vasopressor known,[1] angiotensin II also stimulates the adrenal gland to produce aldosterone. By enhancing renal reabsorption of sodium, aldosterone expands the body's sodium content and plasma volume. This reduces renin production and closes the loops of the negative feedback system. A breakdown in this system may result in higher levels of renin and angiotensin II—and sustained high blood pressure.

Disturbances in other mechanisms can also trigger metabolic chains of events that lead to hypertension. This increasing knowledge has generated interest in drugs designed to halt the hypertensive process at several points. One of the newest drugs is thought to inhibit the enzyme that converts angiotensin I into angiotensin II.[1] Equally important has been the development of more accurate diagnostic tests for "biochemical" profiling.

How useful is measuring renin activity? Some clinicians now advocate "renin profiling" of all hypertensives. This rather complicated test provides the renin-sodium index by indirectly measuring the renin level and comparing it to sodium intake. The index helps distinguish renin-dependent hypertensives (about 70% of patients) from those who are sodium-dependent. It is only the latter who are most likely to benefit from diuretics and the "stepped-care" approach.

While renin profiling can be very useful for selected patients, most physicians consider it unnecessary or impractical for routine evaluation. The initial choice of therapy rarely hinges on renin activity.[2] Also, the renin-sodium index is hard to obtain in non-hospitalized patients and may not offer any real advantages over a therapeutic trial that includes a diuretic (for low-renin patients) or a beta blocker (for high-renin patients).[2,3]

The lab workup that works for most patients Some authorities believe that a minimal workup is sufficient for roughly 90% of hypertensive patients.[3] This generally includes a hematologic profile, urinalysis, blood chemistry (covering a number of biochemical variables), along with the standard ECG and chest roentgenogram.[2,3] More exhaustive tests—including renal profiling, intravenous urograms and catecholamine level determinations—would only be ordered if secondary causes are suspected.

THE "PSYCHOLOGICAL PROFILE" ADDS VALUABLE INSIGHTS

At times, it reveals excessive anxiety A good deal of research has focused on the contributory role of psychological and social factors in the development of hypertension. Such factors have been found to increase plasma renin activity.[4] Consequently it is often recommended that some form of psychosocial profile be added to the patient's family and medical history.[2,5] Even though the hypertensive patient may seem calm, a few carefully worded questions often uncover intense psychic tension. The patient's anxiety may center on his psychological problems alone or may extend to the economic and social repercussions of his illness.

How psychological factors may affect the course of therapy Hypertensive patients with psychological problems may have difficulty in coping with the do's and don'ts of their therapeutic program... and with demoralizing new self-images as "chronically sick, potentially dependent" persons. The psychological profile helps the physician assess the patient's understanding of his illness, his emotional reactions to it, and the likelihood of his compliance with recommended therapy. This information can help set the stage for the mutually rewarding doctor-patient rapport essential to successful long-term management of any chronic illness.

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References: 1. Fighting high blood pressure with consciousness-raising, drug innovation and new zeal for dieting. *Med World News 20*(13):34-44, June 25, 1979. **2.** Caldwell JR: *Postgrad Med 65*(5): 66-77, May 1979. **3.** Rakel RE, *et al*: *Primary Cardiol 5*: 102-109, Sept 1979. **4.** Clamage DM, Vander AJ, Nouw DR: *Psychosom Med 39*: 393-401, Nov-Dec 1977. **5.** Perloff D: *Geriatrics 31*: 77-83, Jan 1976.

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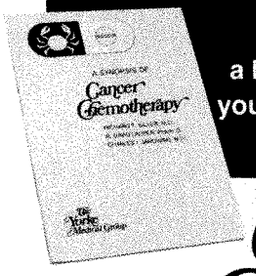

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73 Predicting Cardiac Morbidity Based on Risk Factors and Coronary Angiographic Findings

JOEL E. DIMSDALE, JOHN GILBERT, ADOLPH M. HUTTER, THOMAS P. HACKETT and PETER C. BLOCK

Follow-up analysis of a cohort of 189 men for 1 year after coronary angiography reveals that 25 percent experienced a substantial cardiac morbid event—hospitalization, myocardial infarction, resuscitation or death. The most important risk factors for increased morbidity included severity of angina, history of myocardial infarction, family history of heart disease, fatigue and absence of type A behavior. For the medically treated group alone, the presence of electrocardiographic Q waves, age, stress and low level of acknowledgment of anger were discriminating variables. For the whole group the depression and low serum cholesterol were discriminating variables; the number of diseased vessels was not.

PEDIATRIC CARDIOLOGY

77 Lung Biopsy With Frozen Section as a Diagnostic Aid in Patients With Congenital Heart Defects

MARLENE RABINOVITCH, ALDO R. CASTANEDA and LYNNE REID

Assessment of pulmonary arterial development and structure by lung biopsy with frozen section proved helpful in deciding between a palliative and corrective surgical procedure in eight patients with congenital heart defects and equivocal preoperative hemodynamic data. Such morphologic assessment can be and was related to the degree of hemodynamic distribution of the circulation. As a result of the biopsy, six of the eight patients underwent corrective surgery and two a palliative procedure. Analysis of the pulmonary vascular changes was similar on the frozen and the paraffin-embedded sections. Postoperative hemodynamic data in four patients undergoing corrective surgery revealed either a significant reduction in pulmonary vascular resistance or return to a normal level of pulmonary arterial pressure and no change in the one patient who underwent a palliative procedure.

85 Ventricular Septal Defect in Infancy: Detection With Two Dimensional Echocardiography

JOHN P. CHEATHAM, LARRY A. LATSON and HOWARD P. GUTGESELL

In this study of 53 infants under 1 year of age two dimensional echocardiography detected approximately three fourths of ventricular septal defects large enough to warrant cardiac catheterization in the 1st year of life. Among the 27 patients with a ventricular septal defect, the lesion was correctly identified in 20 (74 percent) and was undetected in 7. No defect less than 4 mm in diameter was detected. False positive diagnoses were related to dropout of echoes in the membranous septum when imaging in the four chamber views. Factors affecting the sensitivity of two dimensional echocardiography in the detection of ventricular septal defects include the resolution of the ultrasonic equipment, the anatomic location of the defect, the composition of the study group and the skill and bias of the ultrasonographer. This technique appears most useful when other cardiac anomalies may mask a large ventricular septal defect.

90 Postnatal Endocardial Fibroelastosis of the Valve of the Foramen Ovale

GROVER M. HUTCHINS, G. WILLIAM MOORE, JOCELYN F. JONES and STEPHEN T. MILLER

Examination of 200 hearts from embryos, fetuses and necropsy patients supports the concept that the postnatal fibroelastotic thickening of the foramen ovale valve endocardial tissue is a nonspecific response of the living to increased mural tension. In changing from a passive structure in the transseptal bloodstream into a barrier of the orifice of the foramen ovale, the valve becomes subject to the tension that acts on the atrial wall. The thickness of the valve increases slowly until birth, abruptly thickens in the newborn period and then returns to a pattern of slow, steady increase.

continued on page A35

QUICK QUIZ

Fig. 1

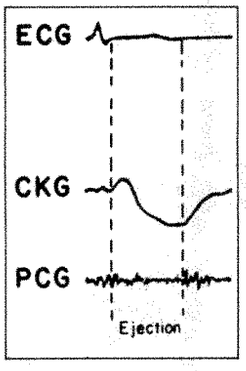

Fig. 2

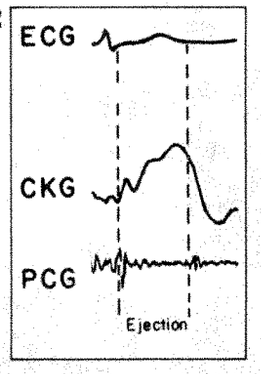

Fig. 3

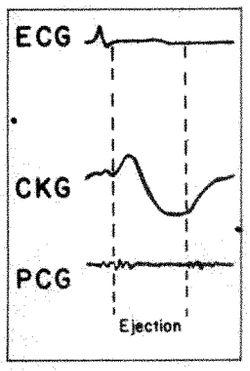

Fig. 4

I. Figure 1 is a pre-stress CKG™ (Cardiokymograph) tracing of the left ventricle (V3 position), it demonstrates:*

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

II. Figure 2 is a two minute post-stress CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

III. Figure 3 is a thirty minute post-stress resting CKG (Cardiokymograph) tracing of the left ventricle (V3 position), on the same patient, demonstrating:

- ☐ A. normal systolic inward motion
- ☐ B. midsystolic bulging
- ☐ C. holosystolic outward motion
- ☐ D. other

IV. Figures 1, 2 and 3, taken together, demonstrate:

- ☐ A. stress induced ventricular wall motion abnormalities consistent with ischemia
- ☐ B. normal ventricular wall motion

V. According to recently published(1) data, the CKG (Cardiokymograph) stress test is:

- ☐ A. 98% sensitive—98% specific
- ☐ B. 59% sensitive—69% specific
- ☐ C. 74% sensitive—95% specific
- ☐ D. 40% sensitive—60% specific

VI. Figure 4 is a photograph of:

- ☐ A. CKG/700 (Cardiokymograph)
- ☐ B. a noninvasive device that provides an analog representation of wall motion
- ☐ C. a low cost, simple device to be used in conjunction with stress testing to enhance diagnostic accuracy
- ☐ D. all of the above

REFERENCE

(1)Silverberg R A, Diamond G A, Vas R, Tzivoni D, Swan H J C, Forrester J S: Noninvasive Diagnosis of Coronary Artery Disease: The Cardiokymographic Stress Test. Circulation. Vol. 61, No. 3, pgs. 579-589.

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QUICK QUIZ—ANSWERS

I. A. normal systolic inward motion II. C. holosystolic outward motion III. A. normal systolic inward motion IV. A. stress induced ventricular wall motion abnormalities consistent with ischemia V. C. 74% sensitive—95% specific VI. D. all of the above

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Guest Editor: **Charles E. Rackley, MD,** Professor of Medicine, Division of Cardiology, University of Alabama School of Medicine, Birmingham, Alabama.

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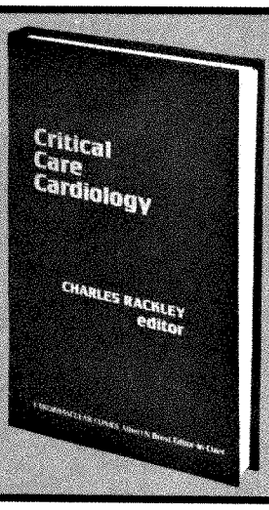

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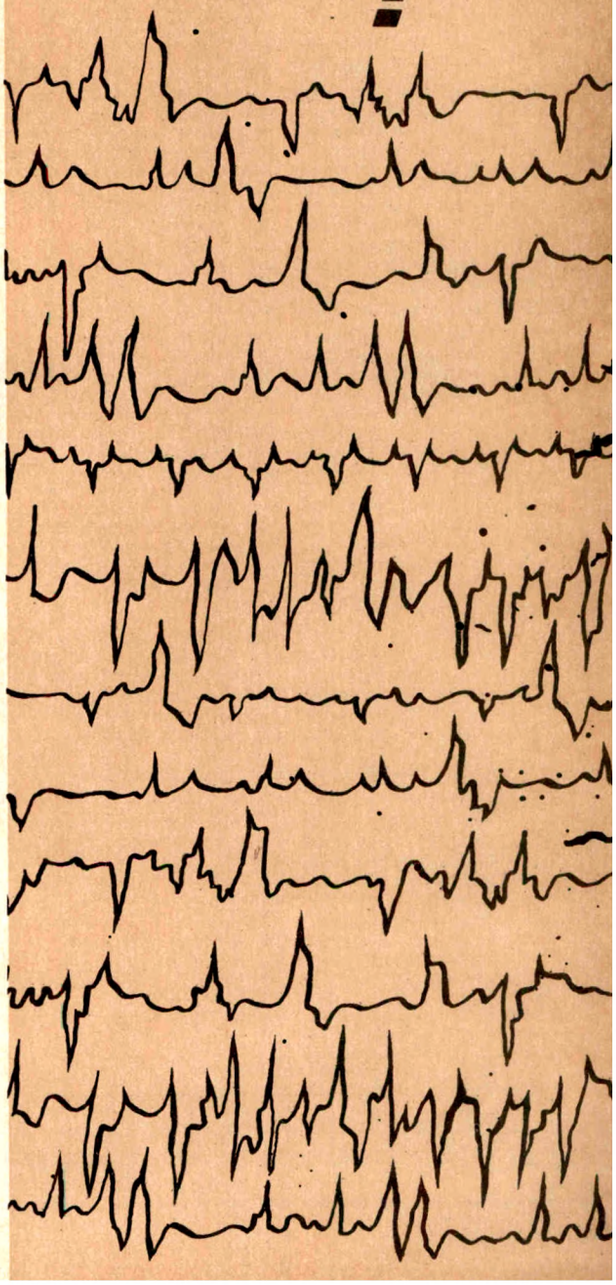

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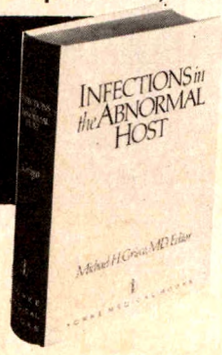

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Oral Norpace has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.* ***Contraindications:*** *Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.* ***Warnings: Norpace may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. 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The concomitant use of Norpace with other Type 1 antiarrhythmic agents should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction. Patients receiving more than one antiarrhythmic drug must be carefully monitored. If first-degree heart block develops, the dosage of Norpace should be reduced. If the block persists, continuation of Norpace must depend upon an assessment of benefit versus risk. Development of second- or third-degree AV block or uni-, bi- or trifascicular block requires discontinuation of Norpace, unless the ventricular rate is adequately controlled by a pacemaker. Because of its anticholinergic activity, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.*** ***Precautions:*** *Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace therapy. Safe use in pregnancy has not been established. Disopyramide has been found in human fetal blood.* ***Norpace has been reported to stimulate contractions of the pregnant uterus.*** *Use of Norpace in pregnant women requires that the potential benefit be weighed against possible hazards to the fetus. Following oral administration, disopyramide has been found in human milk at a concentration not exceeding that in plasma. If use of the drug is deemed essential, an alternate method of infant feeding should be instituted. Effects of Norpace on the fetus during delivery or on the course of labor and delivery are unknown. 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The usual adult dosage is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients less than 110 pounds (50 kg) the recommended dosage is 100 mg every six hours. If rapid control of arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients less than 110 pounds) is recommended. For patients with cardiomyopathy or possible cardiac decompensation, a loading dose should not be given and the initial dose limited to 100 mg every six hours, with subsequent dosage adjustments made gradually with close monitoring.* ***See current complete prescribing information for dosage recommendations. How Supplied:*** *Capsules containing 100 mg or 150 mg of disopyramide base.*

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References: *1. Data on file, Searle Pharmaceuticals Inc. 2. Leahey, E.B., Jr., and others: The Effect of Quinidine and Other Oral Antiarrhythmic Drugs on Serum Digoxin: A Prospective Study, Ann. Intern. Med. 92:605-608 (May) 1980.*

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REPORTS ON THERAPY

95 Improved Exercise Performance in Persons With Stable Angina Pectoris Receiving Diltiazem

KENNETH F. HOSSACK, ROBERT A. BRUCE with the technical assistance of SHIRLEY TRIMBLE and FUSAKO KUSUMI

In a clinically random, double-blind study of 10 patients with stable angina pectoris, the use of diltiazem, a calcium antagonist drug, in a dosage of 240 mg/day increased the patients' duration of exercise on a treadmill, prolonged their time of exercise to the onset of angina and eliminated their angina as the symptom for limiting exercise. The drug reduced the heart rate at rest and at submaximal exertion, but produced no significant change in maximal heart rate during exercise. During submaximal exercise there was a reduction in diastolic blood pressure but not in systolic pressure. Five of the six patients who continued to take the drug maintained or improved their exercise performance on a follow-up study 8 to 12 months later.

102 Effect of Intravenous and Intracoronary Nitroglycerin on Left Ventricular Wall Motion and Perfusion in Patients with Coronary Artery Disease

M. PATRICIA McEWAN, NEIL D. BERMAN, JOHN E. MORCH, DAVID H. FEIGLIN and PETER R. McLAUGHLIN

In 30 patients with significant left anterior descending coronary artery disease and resting anterior wall asynergy, intravenous and intracoronary nitroglycerin may reverse wall motion asynergy and produce favorable or unfavorable changes in perfusion. Both systemic and intracoronary nitroglycerin improved wall motion of hypokinetic ventricular segments in nearly half of the patients studied. Afterload reduction by either intravenous or intracoronary nitroglycerin appeared to be the common mechanism that improved wall motion. These data suggest that systemic effects of nitroglycerin are the most important in reversing asynergy. A variable response on left ventricular preload, with both decreases and increases in end-diastolic volume, was observed. The ejection fraction increased significantly in patients with reversible asynergy after both intravenous and intracoronary injections of nitroglycerin.

109 Hemodynamic Effects of Molsidomine at Rest and During Submaximal and Maximal Exercise in Patients With Coronary Artery Disease Limited by Exertional Angina Pectoris

JEAN-MARIE R. DETRY, JACQUES MELIN, LUCIEN A. BRASSEUR, JACQUES COSYNS and MICHEL F. ROUSSEAU

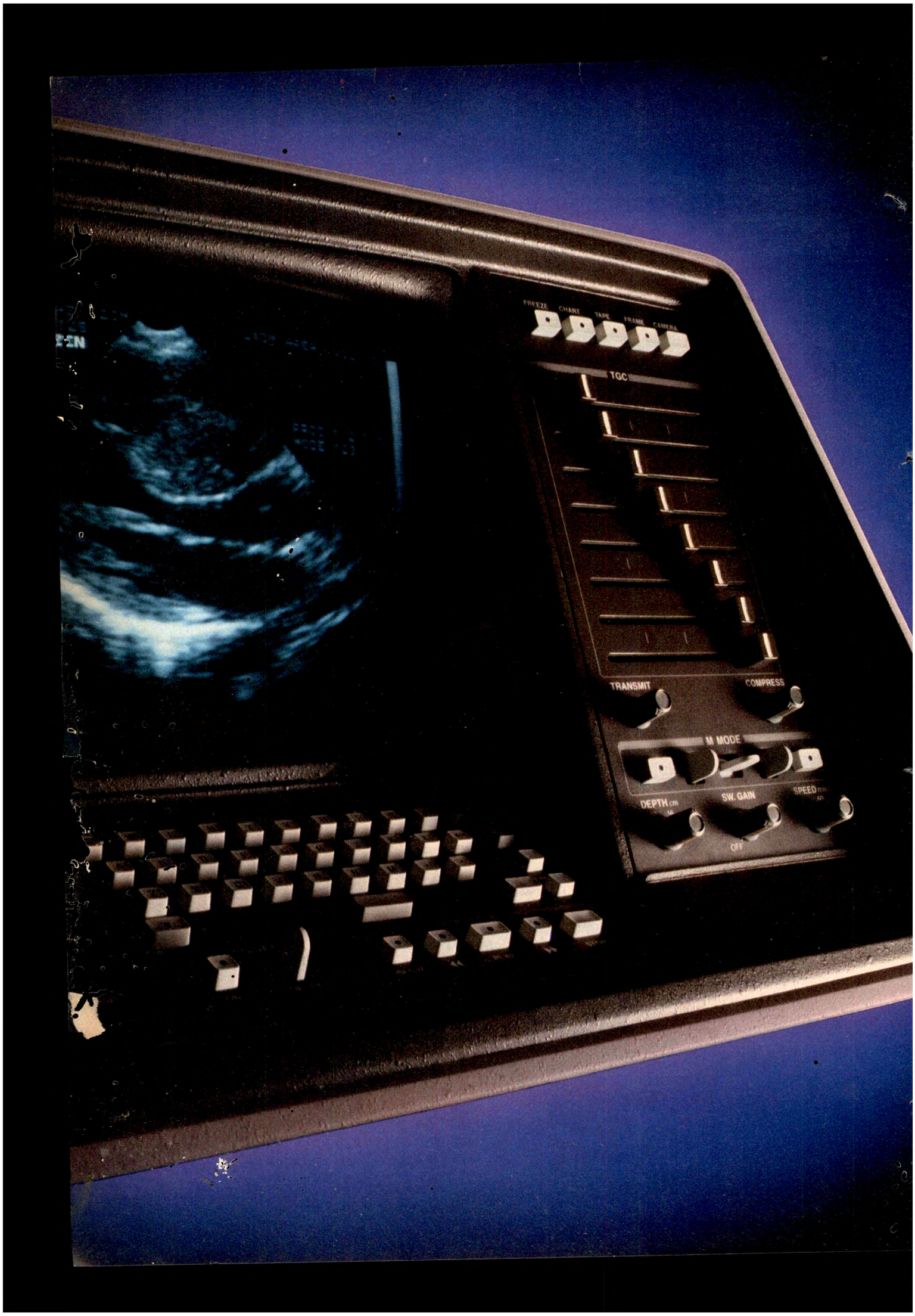
Molsidomine, a new antianginal drug studied in 10 patients with coronary artery disease and exertional angina pectoris, increased heart rate and decreased cardiac output and mean systemic and pulmonary arterial pressures at rest and during submaximal exercise. Its hemodynamic mechanisms of action that improved exercise tolerance in 60 percent of the patients resemble those of nitrates and include a decrease in venous and arterial tone that lasts 5 to 8 hours after oral, sublingual or intravenous administration. The prevention of angina pectoris in 60 percent of the patients after molsidomine was attended by a marked decrease in the mean pulmonary arterial pressure, no change in cardiac output and lower mean arterial pressure and systemic vascular resistance.

116 Hemodynamics at Rest and During Exercise After Oral Hydralazine in Patients With Cor Pulmonale

LEWIS J. RUBIN and ROBERT H. PETER

This hemodynamic study of 12 patients with chronic cor pulmonale indicates that the lung vascular bed in some patients responds to oral hydralazine with a reduction in pulmonary resistance and an increase in cardiac output both at rest and during exercise. During exercise, the stroke volume increased by 30 percent. Mean systemic blood pressure and heart rate were not appreciably changed. These 12 patients with parenchymal lung disease and pulmonary hypertension showed an increased oxygen delivery to the tissue at a lower right ventricular afterload both at rest and during exercise after being treated with oral hydralazine. No adverse effects limited the drug's use. The use of effective vasodilators may prove helpful in the management of cor pulmonale, although it is not known if they will alter the clinical course of patients with this condition.

continued on page A38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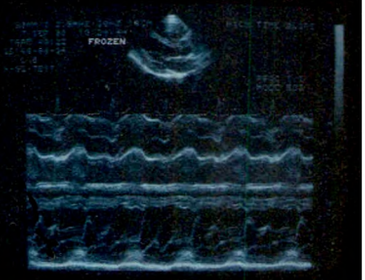

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123 **Clinical Pharmacology and Antiarrhythmic Efficacy of N-Acetylprocainamide**

ROGER A. WINKLE, PATRICE JAILLON, ROBERT E. KATES and FLORA PETERS

N-Acetylprocainamide (NAPA), the major metabolite of procainamide, suppressed chronic ventricular ectopic complexes without adverse effects in only a minority of the 11 patients with chronic ventricular arrhythmias. The investigators were able to achieve 90 percent suppression of ventricular ectopic complexes in only 2 of 11 patients. Several patients unsuccessfully treated with NAPA have subsequently had arrhythmias successfully suppressed with other new antiarrhythmic compounds. Adverse effects included an allergic rash in one patient, gastrointestinal symptoms in seven patients and visual symptoms in four patients at plasma concentrations as low as 6.9 mg/ml. This study also demonstrated that the drug differs electrophysiologically from procainamide, obeys linear pharmacokinetics over the clinically tolerated range of oral doses, and its antiarrhythmic action may have little relation with the antiarrhythmic response observed during long-term therapy with procainamide. The ultimate role of NAPA remains to be defined.

131 **Mexiletine for Refractory-Ventricular Arrhythmias: Results Using Serial Electrophysiologic Testing**

JOHN P. DiMARCO, HASAN GARAN and JEREMY N. RUSKIN

The administration of mexiletine during serial drug testing to 35 patients with electrically inducible ventricular arrhythmias and to 6 patients with recurrent ventricular tachycardia that could not be induced or terminated by programmed cardiac stimulation demonstrates that the drug provides well tolerated effective prophylaxis against recurrent ventricular arrhythmias in a significant proportion (42 percent) of patients resistant to conventional antiarrhythmic drugs. All patients had arrhythmias resistant to all conventionally available agents. Severe adverse neurologic effects (dysphagia, ataxia and disabling tremor) occurred early during mexiletine therapy in 3 patients, but none occurred in the 24 patients discharged on long-term therapy. The administration of mexiletine was discontinued in four patients who had spontaneous ventricular tachycardia within 48 hours after the start of mexiletine therapy. Mexiletine is a promising new antiarrhythmic drug capable of suppressing ventricular arrhythmias resistant to conventionally available drugs. Electrically induced tachycardias not inducible by programmed stimulation seem most likely to respond favorably.

139 **Electrophysiologic Effects of Ouabain in Patients With Preexcitation and Circus Movement Tachycardia**

RAMESH C. DHINGRA, EDWIN V. PALILEO, BORIS STRASBERG, STEVEN SWIRYN, ROBERT BAUERNFEIND, CHRISTOPHER WYNDHAM and KENNETH M. ROSEN

Because intravenously administered ouabain did not significantly affect anterograde or retrograde anomalous pathway refractoriness in 19 patients with an anomalous conduction pathway, and did not interfere with induction of tachycardia in most patients with preexcitation, use of oral glycosides alone appears to be of limited value in patients with preexcitation and recurrent supraventricular tachycardia. In this study, sustained atrioventricular (A-V) reentrant paroxysmal supraventricular tachycardia was inducible in all 19 patients before and in 17 patients (89 percent) after ouabain. Intravenously administered ouabain significantly increased the cycle length of induced tachycardia by depressing A-V nodal conduction, and tachycardia could not be induced in two patients because of this increased A-V nodal refractoriness. The lack of significant effect of digitalis on anomalous pathway refractoriness coupled with a possible increase in ventricular vulnerability to ventricular fibrillation suggests that this agent would be dangerous in patients with paroxysmal atrial fibrillation complicating preexcitation with a short anomalous pathway.

REVIEWS

145 **Observations on Detecting Left Ventricular Thrombus With Two Dimensional Echocardiography: Emphasis on Avoidance of False Positive Diagnosis**

RICHARD W. ASINGER, FRANK L. MIKELL, BIM SHARMA, MORRISON HODGES with the technical assistance of LILLIAN MICHAUD, JOE ELSPERGER, DARCIE BASS and KIM KARLSON

Two dimensional echocardiography can potentially detect left ventricular thrombus before embolization and make it possible to institute appropriate therapy in patients after infarction and to prevent or decrease the incidence of embolization. In this series of 2,657 consecutive two dimensional echocardiographic studies, 41 patients had echocardiographic findings highly suggestive (n = 25) or characteristic (n = 16) of left ventricular thrombus. In seven patients, left ventriculography demonstrated apical filling defects consistent with thrombus within 1 week of the two dimensional echocardiogram. Six patients had a surgical procedure that confirmed or supported the echocardiographic diagnosis of left ventricular thrombus. All patients had wall motion abnormalities adjacent to their thrombus. These results indicated that two dimensional echocardiography allows detection of left ventricular thrombi that might not be clinically manifest or detected by other available methods. A practical grading scale is presented that indicates the index of suspicion for left ventricular thrombus and minimizes false positive examinations.

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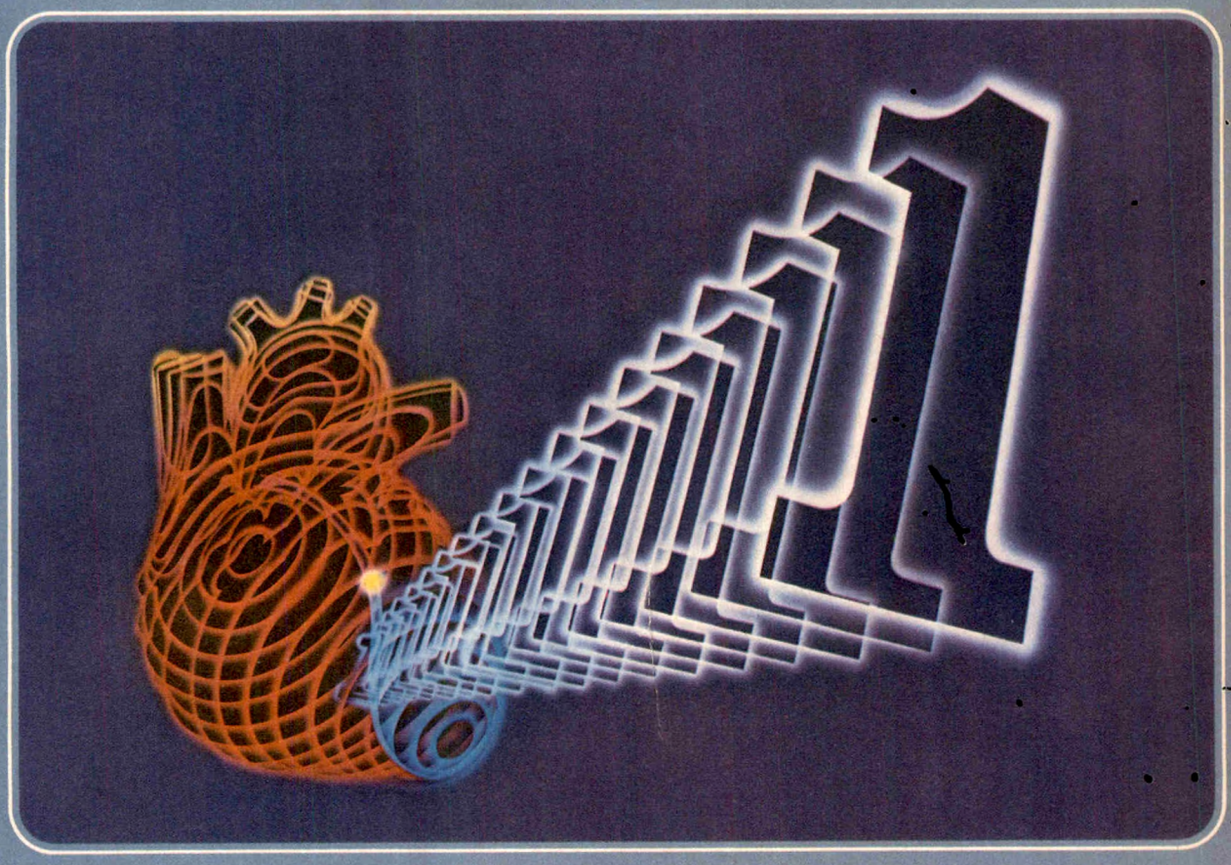

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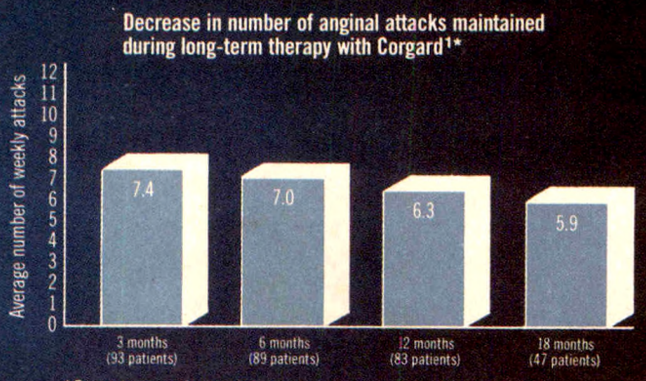

*Seventeen patients also received long-acting nitrates and/or dipyridamole at some time during the long-term therapy period.

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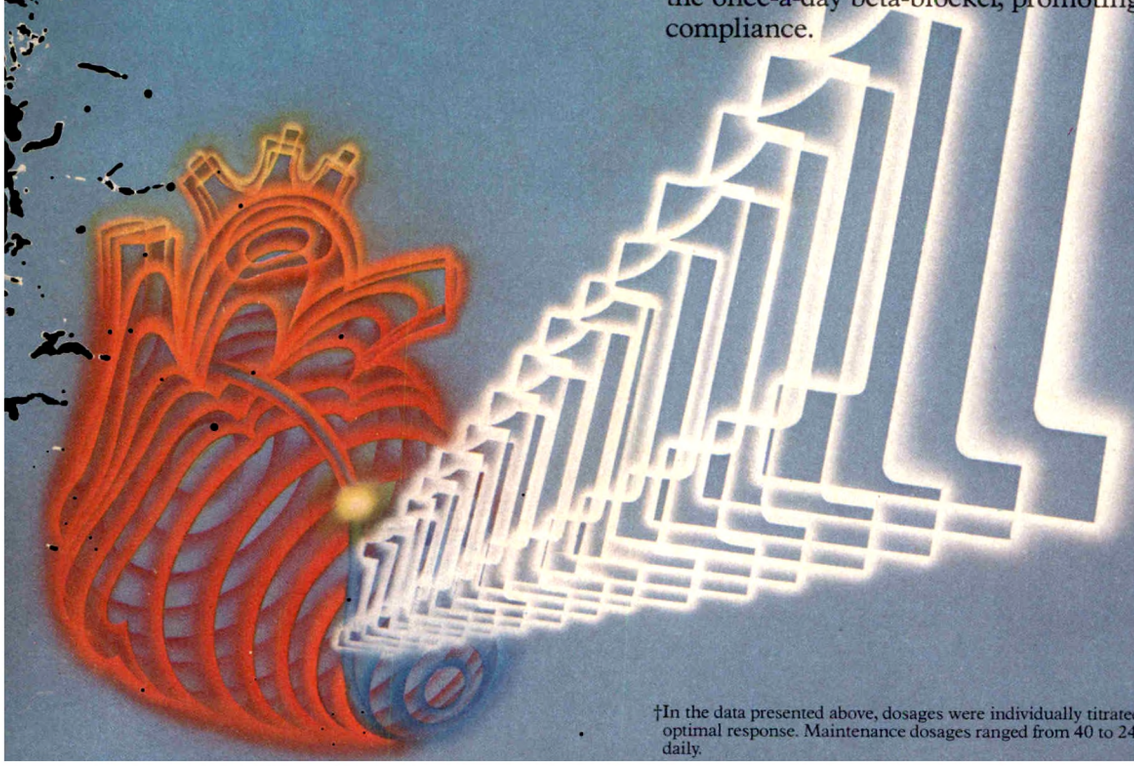
Once-a-day, everyday, Corgard offers round-the-clock protection

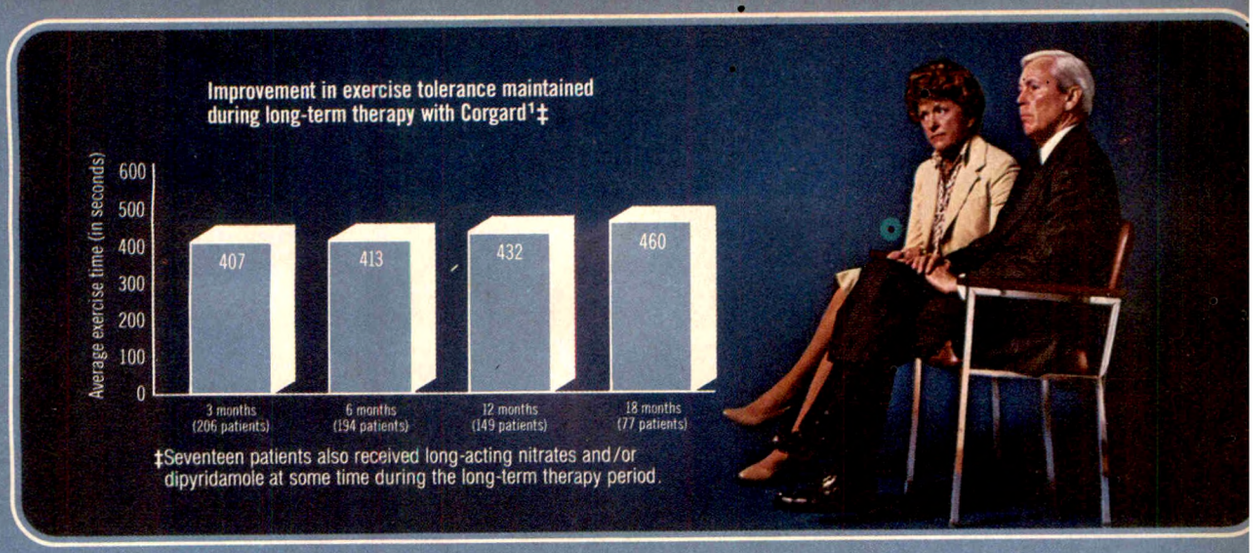
A single daily dose of Corgard offers prophylaxis in angina pectoris, helping to protect the patient all day and all night from painful attacks. And in extended clinical studies, the efficacy of Corgard — as demonstrated by a decreased rate of anginal attacks and an increase in exercise tolerance — was maintained.[1]

Once-a-day, everyday, Corgard decreases the frequency of anginal attacks

Corgard taken just once daily offers round-the-clock protection from angina pain. In one short-term study, Corgard, once a day, decreased the average number of anginal attacks per week in 115 patients with angina, from 13.6 pretherapy to 6.4 at the end of 14 weeks of therapy, a mean decrease of 59%.[1†] In 19% of the 115 patients, anginal attacks were completely eliminated. And the long half-life (20 to 24 hours) makes Corgard the once-a-day beta-blocker, promoting patient compliance.



†In the data presented above, dosages were individually titrated to achieve optimal response. Maintenance dosages ranged from 40 to 240 mg Corgard daily.



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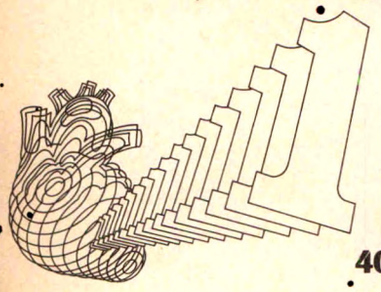

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in the presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

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Reference:

1. Data on file, Squibb Institute for Medical Research.

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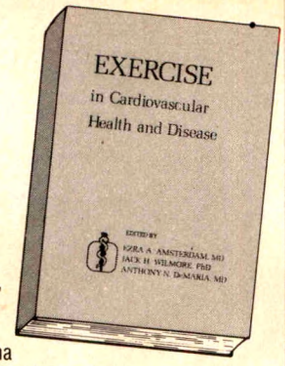

Edited by
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57 **Therapy of Coronary Vasoconstriction in Patients With Coronary Artery Disease**

STEPHEN GUNTHER, JAMES E. MULLER, GILBERT H. MUDGE, Jr. and WILLIAM GROSSMAN

Nifedipine, 10 mg given buccally, prevented the increase in coronary vascular resistance during the cold pressor test in 10 of 10 patients with coronary artery disease. The response in five patients treated with placebo remained unchanged. This dose had no effect on systemic hemodynamics or myocardial oxygen consumption either at rest or during the cold pressor test. At this dose, nifedipine appeared to exert a selective, antivasoconstrictive effect on the coronary circulation and was well tolerated without side effects by all patients. Of the antianginal drugs, calcium antagonists appear to be most effective in preventing coronary vasoconstriction.

63 **Nifedipine in the Treatment of Unstable Angina, Coronary Spasm and Myocardial Ischemia**

PAUL G. HUGENHOLTZ, HERMAN R. MICHELS, PATRICK W. SERRUYS and RON W. BROWER

Intracoronary injection of nifedipine promptly reversed provoked or spontaneous coronary spasm in five of six patients studied in the cardiac catheterization laboratory. In other patients, intracoronary injection was associated with virtual cessation of local mechanical cardiac action and thinning of the ventricular wall during systole, which indicated a specific inhibitory action on contractile energy expenditure in the presence of increased coronary flow. Coronary arteriography demonstrated severe atherosclerotic coronary artery disease in 14 of 20 patients who responded promptly to nifedipine. These and other results in 31 patients with symptomatic unstable angina led the investigators to recommend that nifedipine should be added to beta adrenergic blockade therapy if the latter does not appear immediately effective. This combination has not been shown to cause adverse hemodynamic effects.

74 **Treatment of Prinzmetal's Variant Angina. Role of Medical Treatment With Nifedipine and Surgical Coronary Revascularization Combined With Plexectomy**

MICHEL E. BERTRAND, JEAN M. LABLANCHE and PIERRE Y. TILMANT

This study suggests the following emerging strategy for the treatment of Prinzmetal's angina: Intravenous, or preferably intracoronary, injection of nitroglycerin is the basic therapy for spasm that occurs during coronary arteriography (although intracoronary injection of 0.2 mg of nifedipine may be beneficial); coronary arterial bypass grafting combined with partial denervation of the heart for patients with fixed arteriosclerotic lesions and superimposed spasm; and calcium antagonists for patients with angiographically normal coronary arteries. In these 70 patients with Prinzmetal's angina 29 percent had angiographically normal coronary arteries and the remainder had fixed atherosclerotic lesions.

Ergonovine Testing to Detect Spontaneous Remissions of Variant Angina During Long-Term Treatment With Calcium Antagonist Drugs

DAVID D. WATERS, JADWIGA SZLACHCIC, PIERRE THEROUX, FRANZ DAUWE and HENRY F. MIZGALA

In this subgroup of 22 patients with variant angina and an initially positive ergonovine test who had responded well to calcium antagonist drugs, all were free from anginal attacks while taking the drugs. After medication was discontinued, 12 patients did not have angina or S-T segment shifts during a second ergonovine test to a maximal dose of 0.4 mg. All 12 also remained free of variant anginal attacks without these drugs, 4.2 ± 2.9 months later. The patients whose tests reverted to negative could not be differentiated by other clinical variables from those whose tests remained positive. These results indicate that ergonovine testing is helpful in identifying patients with variant angina in whom treatment with calcium antagonist drugs can probably be safely discontinued.

HISTORICAL MILESTONES

5 **The Frustrated Benevolance of "Dr. Anonymous"**

PAUL KLIGFIELD

This month's Milestone blows the cover of the mysterious Dr. Anonymous of Chester and provides the reader with examples of Dr. Heberden's skill as a masterful physician and English writer. For a real learning experience, try writing your own short description of angina pectoris and then compare it with Heberden's.

SPECIAL DEPARTMENTS

8 **Books Received**

9 **American College of Cardiology News**

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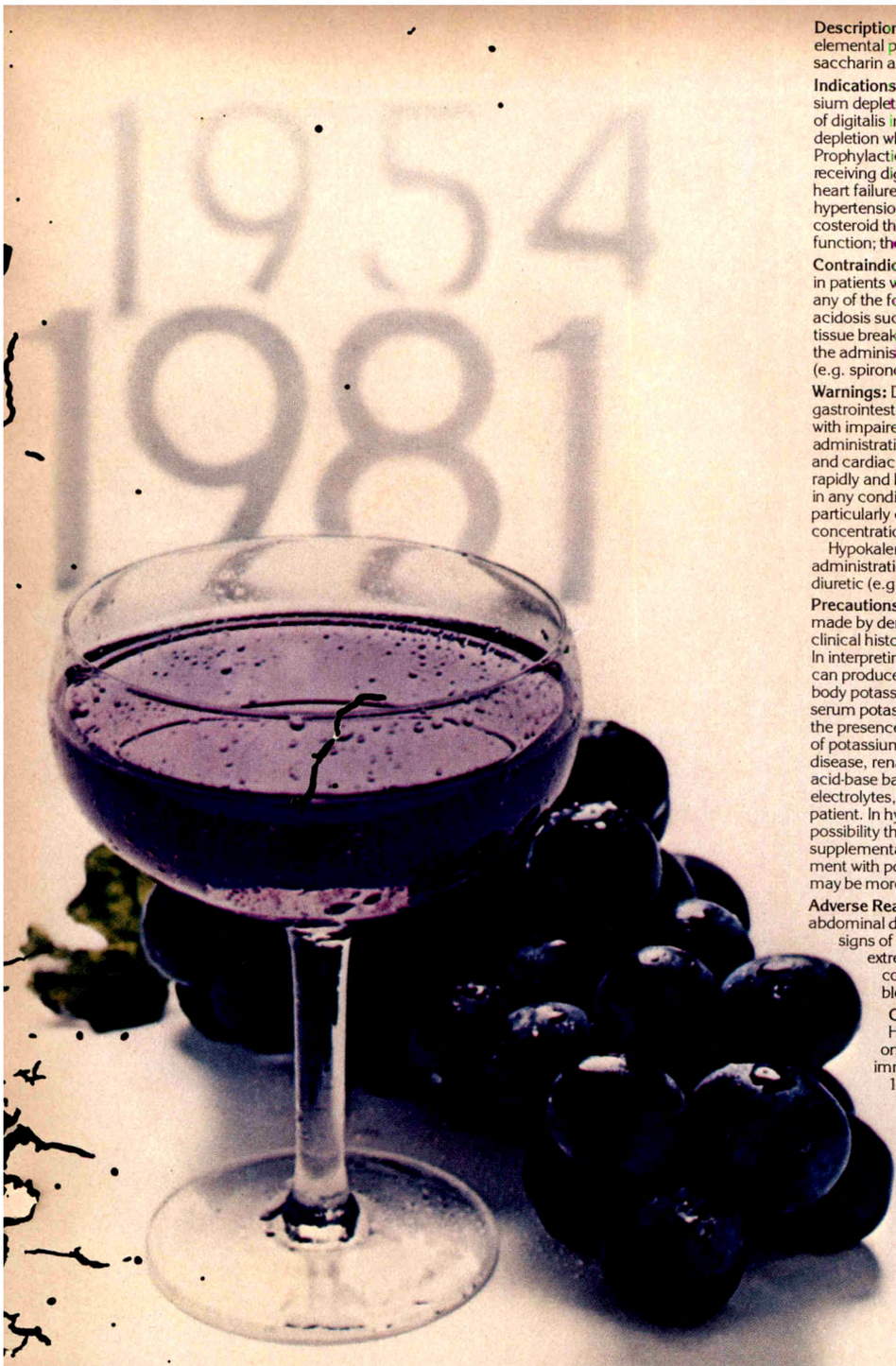

Description: Each 15 ml (tablespoonful) supplies 20 mEq of elemental potassium (as potassium gluconate, 4.68 g) with saccharin and aromatics. Alcohol 5%.

Indications: Kaon Elixir is indicated for the treatment of potassium depletion in patients with hypokalemia, for the treatment of digitalis intoxication, and for the prevention of potassium depletion when the dietary intake of potassium is inadequate. Prophylactic administration may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure; hepatic cirrhosis with ascites; patients with hypertension on long-term diuretic therapy; patients on corticosteroid therapy; hyperaldosteronism states with normal renal function; the nephrotic syndrome; and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g. spironolactone, triamterene).

Warnings: Do not administer full strength. Kaon Elixir may cause gastrointestinal irritation if administered undiluted. In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in any condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g. spironolactone or triamterene).

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient. In hypokalemic states, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In these circumstances, potassium replacement with potassium chloride (e.g. Kaochlor 10% Liquid, W-T) may be more advantageous than with other potassium salts.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias, and heart block.

Overdosage and Treatment of Hyperkalemia: Hyperkalemia can occur from overdosage or during one of several medical conditions. It should be treated immediately by one or more of the following: 1) Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml. 2) administration of sodium or ammonium cycle exchange resins orally or as retention enemas; 3) hemodialysis or peritoneal dialysis; 4) elimination of potassium containing foods. Caution: Digitalis toxicity can occur if the serum potassium is lowered too rapidly.

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INDICATIONS:

1. Congestive heart failure: Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. Atrial fibrillation: Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. Atrial flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. Paroxysmal atrial tachycardia: Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. Cardiogenic shock: The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.

Ventricular fibrillation.

WARNINGS:

> Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:

Gynecomastia: Uncommon.

Overdose or toxic effects in adults:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage.

Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:

Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram; see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.

Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.
Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.
Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.
Children, over 10 years of age, require adult dosages in proportion to their body weight.
Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

Gated Cardiac Blood Pool Imaging and Thallium-201 Myocardial Scintigraphy for Detection of Remote Myocardial Infarction

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The primary goal of this study was to assess the frequency of persistent regional wall motion abnormalities and myocardial perfusion defects detectable late after myocardial infarction with radionuclide ventriculography and thallium-201 imaging, respectively. The study was performed prospectively in 32 patients in whom infarct size was estimated enzymatically at the time of the acute episode and in 10 patients without infarction. Thallium-201 imaging and radionuclide ventriculography were performed with the patient at rest an average of 11 months after infarction (range 6 to 20 months) and analyzed independently by two observers who were unaware of results of other clinical and laboratory data. Perfusion defects were detected in 94 percent (30 of 32) by observer I and in 91 percent (29 of 32) by observer II. Wall motion abnormalities were detected in 78 percent (25 of 32) and 75 percent (24 of 32) by observers I and II, respectively, but in 10 of the patients with an infarct size less than 20 creatine kinase-gram-equivalents (CK-g-eq), wall motion abnormalities were found in only 50 and 40 percent, respectively, by these observers ($p < 0.04$). Electrocardiographic changes of infarction (Q waves) were present in only 56 percent (18 of 32) of patients. Sixty-eight percent of patients with an infarct size greater than 20 CK-g-eq had persistent Q waves but these were present in only 30 percent with an infarct size less than 20 CK-g-eq ($p < 0.04$). The sites of perfusion defects and of wall motion abnormalities corresponded closely and were concordant with electrocardiographic localization. Thus, thallium-201 imaging and radionuclide ventriculography are sensitive noninvasive techniques for identifying prior myocardial infarction, and are particularly helpful in patients with conduction abnormalities or equivocal electrocardiographic findings.

From the Cardiovascular Division, Department of Internal Medicine and the Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri. This work was supported in part by Grant HL17646 from the Specialized Centers of Research in Ischemic Heart Disease, the National Institutes of Health, Bethesda, Maryland. Manuscript received February 25, 1980; revised manuscript received July 1, 1980, accepted July 3, 1980.

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The diagnosis or exclusion of remote myocardial infarction is a common and difficult problem in clinical medicine. If infarction is not documented at the time of the acute event, subsequent diagnosis frequently depends on recognition of electrocardiographic Q waves or demonstration of coronary arterial lesions and associated regional wall motion abnormalities at cardiac catheterization. A sensitive noninvasive index of prior myocardial infarction would be of considerable value in determining prognosis and facilitating management of patients, particularly those with congestive heart failure of occult origin, underlying conduction disturbances or a questionable clinical history of remote infarction.

Nuclear medicine techniques, including thallium-201 and technetium-99m pyrophosphate imaging[1–6] and, more recently, gated blood pool scintigraphy,[7–10] are assuming an increasing role in the diagnosis and assessment of acute myocardial infarction. However, the utility of these techniques in detecting remote myocardial infarction has not been thoroughly characterized in patients with infarction defined prospectively and in whom the extent of damage was quantified at the time of the acute episode. Accordingly, this prospective study was undertaken in patients with infarction documented and quantified initially by enzymatic estimation. We assessed the frequency of persistent regional wall motion abnormalities detectable with radionuclide ventriculography and of focal myocardial perfusion defects detectable with thallium-201 imaging 5 to 20 months after the acute episode.

Methods

Study Patients

The study group comprised 32 patients admitted with an initial myocardial infarction documented by a typical clinical history, acute electrocardiographic changes and elevation of plasma MB creatine kinase activity[11]; on the basis of electrocardiogram and history, all were found during follow-up study to have sustained no additional infarction. In addition, 9 of these patients had undergone technetium-99m pyrophosphate scintigraphy at the time of their admission for acute myocardial infarction. In all patients infarct size was estimated enzymatically from analysis of serial changes of plasma creatine kinase activity.[12] The details of the method[12] and its limitations[13,14] can be found in several recent reviews. All of the patients in this study were admitted within 6 hours of symptoms and a complete plasma creatine kinase activity curve was obtained. As noted in the Results, the range of infarct size was wide and virtually identical to the distribution of infarct size among all patients with initial infarction admitted during the interval in which this study was conducted (data not shown). The patients were evaluated 6 to 20 months after infarction and an electrocardiogram, a thallium scintigram and a radionuclide ventriculogram were obtained. Because we sought to detect residual myocardial scar rather than myocardial ischemia, these studies were performed at rest.

Control patients: To evaluate the problem of false positive test results, we studied 10 additional patients who had neither clinical nor electrocardiographic evidence of myocardial infarction and who had undergone cardiac catheterization because of recurrent transitory chest pain. The scintigraphic studies in this group were performed 24 to 48 hours after cardiac catheterization. Informed consent was obtained from all patients.

Diagnosis and localization of infarction: The site of infarction and its designation as either transmural or subendocardial were determined from electrocardiographic findings at the time of the initial hospitalization. Transmural myocardial infarction was defined by either development of new Q waves or marked loss of R waves in comparison with previous tracings. The electrocardiogram taken at the time of the study was considered diagnostic of prior myocardial infarction only if it contained significant Q waves, defined as (1) greater than 40 ms in duration, or (2) 20 to 40 ms in duration and more than 25 percent of the R wave in amplitude. Infarction was classified as inferior if these changes were noted in at least two of the inferior leads (II, III and aVF) and as anterior if they were present in one or more of the leads from V_2 through V_6. Poor R wave progression in the precordial leads without abnormal Q waves was not considered diagnostic of prior anterior myocardial infarction. Subendocardial myocardial infarction was defined as transient S-T and T wave changes at the time of initial hospitalization without subsequent development of Q waves in patients with enzymatically documented acute myocardial infarction.

Radionuclide Studies

Thallium imaging: Myocardial imaging at rest was performed after intravenous administration of 1.0 to 1.6 millicuries (mCi) of thallium-201 thallous chloride. The images were obtained with a standard field (25.4 cm diameter, 0.64 cm thick NaI crystal) scintillation camera (Searle LEM) fitted with a low energy, medium resolution, parallel hole collimator and interfaced to a dedicated minicomputer system (Ohio Nuclear VIP 450). Images were obtained in the anterior, 35° and 60° left anterior oblique and left lateral projections; each image consisted of 250,000 counts. Images were interpreted independently by two experienced observers who were unaware of both the clinical diagnosis and the results of gated blood pool studies. Images were viewed directly on the computer video-display with varying degrees of operator-controlled contrast enhancement. For analysis, the left ventricular myocardium was divided into five anatomic segments (anterior, septal, lateral, inferior and posterior walls) and the location of each defect was recorded.

Radionuclide angiography: Gated blood pool imaging was performed after labeling of the patients' red cells in vivo with technetium-99m.[15] This was accomplished by an intravenous injection of stannous pyrophosphate (7.7 mg) followed 15 to 30 minutes later by the injection of 20 to 25 mCi of technetium-99m. The images were collected with the same scintillation camera and computer system used for thallium scintigraphy. Each study consisted of multiple views including anterior, 30° to 45° left anterior oblique with 15° caudad angulation, and 70° left anterior oblique projections. Multigated acquisition of scintigraphic data was achieved according to the general technique described by Burow et al.[16]; the commercially available system used in this study divided the R-R interval into 32 equal time periods (frames). Each image frame consisted of approximately 250,000 counts.

Left ventricular ejection fraction was determined with a modification of the method of Burow et al.[16] with the use of a semiautomatic computer algorithm supplied by the manufacturer. Briefly, the operator first defined a tissue background region adjacent to the left ventricle after which the computer corrected each of the 32 frames for background activity. Then the operator defined an approximate region of interest surrounding the left ventricle on the end-diastolic frame and for each quadrant of this region selected the activity threshold that best corresponded to the left ventricular edge on this frame. The computer then applied an edge detection algorithm to define a left ventricular region of interest on each image frame and plotted activity in these variable regions versus frame number (time during the cardiac cycle). Ejection fraction was calculated as stroke activity (end-diastolic minus end-systolic activity in the left ventricle) divided by end-diastolic activity. The reliability of this method for determination of ejection fraction has been validated in our laboratory by comparison of the measurements obtained in 31 patients with those estimated from contrast angiography ($r = 0.91$) (unpublished observations).

Regional wall motion was evaluated independently by two observers who did not know the clinical diagnosis or the results of other studies and who interpreted the cinematic images directly on the computer video display. The wall motion of each of the five anatomic segments of the left ventricular wall

was scored subjectively as normal or abnormal (hypokinetic, akinetic or dyskinetic), and the location of each defect recorded.

Statistical analysis: The results for continuous measurements are expressed as mean ± standard deviation. Comparisons of group results were performed by Student's *t* test or chi-square test with continuity correction and correlations were performed by linear regression analysis.

Results

Extent and site of infarction: The 32 patients with prior myocardial infarction included 22 men and 10 women with a mean age of 58 years (range 43 to 76). They were studied between 6 and 20 months (mean 11) after myocardial infarction. The 10 patients without infarction consisted of 8 men and 2 women with a mean age of 55 years (range of 43 to 64). These patients, who were selected on the basis of normal left ventricular function and regional wall motion at cardiac catheterization, had a mean angiographically determined ejection fraction of 0.65 ± 0.7 (range 0.55 to 0.77). Six of these patients had completely normal coronary arteries and four had at least 50 percent stenosis of the diameter of one or more major vessels. One patient had obstruction in the right coronary artery, one in the left anterior descending artery, one in the circumflex artery and one in the left main coronary artery.

Enzymatic estimates of infarct size ranged from 2.5 to 78 creatine kinase-gram-equivalents (CK-g-eq) (Fig. 1). These values ranged from 12 to 78 CK-g-eq among the 12 patients with anterior (including anterolateral) myocardial infarction, from 2.5 to 46 CK-g-eq among the 11 with inferior (including inferoposterior) infarction, and from 5 to 42 CK-g-eq among the 9 with subendocardial infarction. Overall, infarct size was 20 or less CK-g-eq in 10 patients, 21 to 40 CK-g-eq in another 10 and greater than 40 CK-g-eq in the remaining 12.

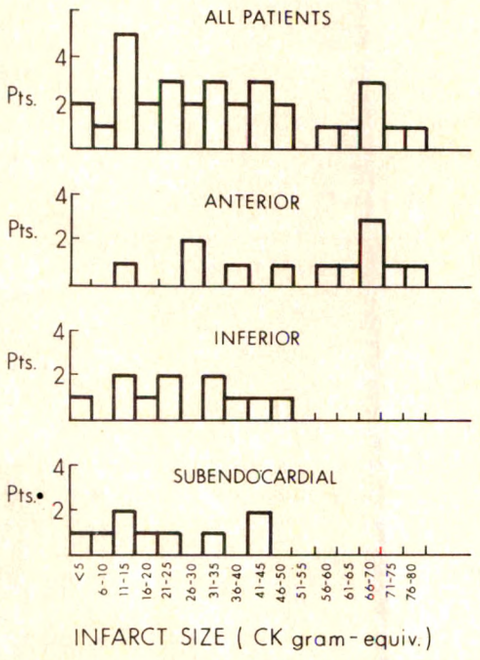

FIGURE 1. Distribution of infarctions according to size (CK-g-eq) and location among the 32 patients with myocardial infarction.

Thallium-201 imaging: Focal defects were seen in thallium-201 images from 29 to 30 of the 32 patients (91 and 94 percent) according to the two observers (Table I). Only 8 of the 10 patients (7 according to observer I) with an infarct size of less than 20 CK-g-eq exhibited a defect on thallium scans. The normal studies occurred in patients with a small inferior myocardial infarct of 2.5, 5 and 14.5 CK-g-eq, respectively (the two observers disagreed on the thallium findings in the patient with an infarct of 14.5 CK-g-eq). In the control patients, one observer interpreted all thallium-201 images as normal whereas the second observer described two (false positive) defects.

Radionuclide ventriculography: The two observers detected regional wall motion abnormalities with radionuclide ventriculography in 25 and 24 (78 and 75 percent) of the 32 patients, respectively (Table I). Among the 10 patients with an infarct size of less than 20 CK-g-eq, only 5 (4 according to observer II) had abnormal wall motion compared with 20 or 22 of those with a larger infarct ($p < 0.05$) (Table I). The patients with normal thallium-201 images also had a normal radionuclide ventriculogram. Normal studies were more frequent in patients with inferior or subendocardial infarction; all but one of the normal studies occurred in patients from these subgroups. In the control studies, one observer found no regional wall motion abnormalities, whereas the other observer interpreted one study as abnormal. Mean ejection fraction determined with radionuclide ventriculography in patients with myocardial infarction was 0.45 ± 0.14 compared with 0.59 ± 0.07 in control patients ($p < 0.05$). Late ejection fraction correlated weakly with initial infarct size estimated enzymatically during the acute phase (Fig. 2).

Follow-up electrocardiographic results: Q waves considered diagnostic of prior myocardial infarction were present on electrocardiograms obtained at the time

TABLE I

Results of Electrocardiographic and Radionuclide Studies in 32 Patients

	Cases (n)	Abnormal Thallium Image	Abnormal Wall Motion	Abnormal Electrocardiogram
All Patients				
Observer I	32	30 (94%)	25 (78%)	18 (56%)
Observer II	32	29 (91%)	24 (75%)	
Patients with infarct size >20 CK-g-eq				
Observer I	22	22 (100%)	20 (91%)	15 (68%)
Observer II	22	22 (100%)	20 (91%)	
Patients with infarct size <20 CK-g-eq				
Observer I	10	8 (80%)	5 (50%)	3 (30%)
Observer II	10	7 (70%)	4 (40%)	
Controls				
Observer I	10	0 (0%)	0 (0%)	0 (0%)
Observer II	10	2 (20%)	1 (10%)	

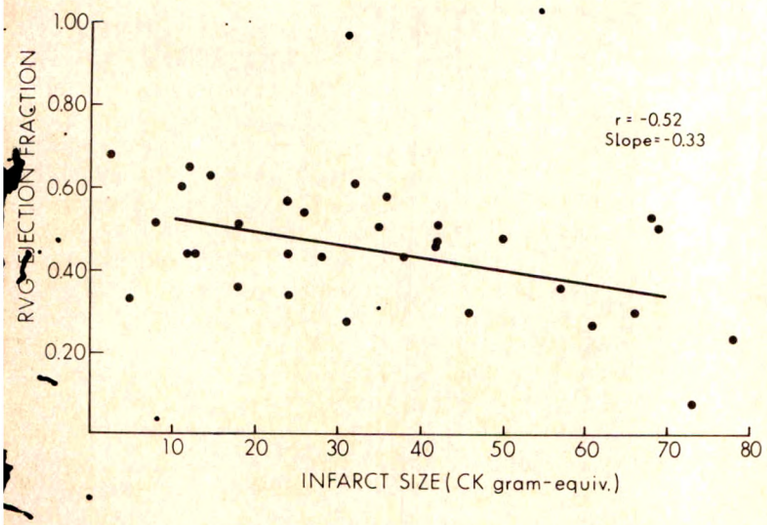

FIGURE 2. Relation between ejection fraction determined by radionuclide ventriculography (RVG) and infarct size estimated enzymatically.

of the follow-up radionuclide studies among 18 (56 percent) of the 32 patients (Table I). Thus, electrocardiography is much less sensitive for detection of remote myocardial infarction than either thallium-201 imaging ($p < 0.002$) or radionuclide ventriculography ($p < 0.03$). More patients (68 percent) with an enzymatically estimated infarct size greater than 20 CK-g-eq had persistent Q waves at the time of follow-up study than patients with an infarct size less than 20 CK-g-eq (30 percent) ($p < 0.04$). There was no significant difference in mean infarct size in the patients with loss of R wave amplitude or with transient Q waves compared with those with subendocardial infarction defined electrocardiographically at the time of the initial episode. Among the five patients with transmural myocardial infarction at the time of the initial episode who did not have Q waves at follow-up study, two had had Q waves at the time of their myocardial infarction that subsequently resolved. The other three patients did not have Q waves initially but did have serial decreases in R wave voltage.

Myocardial infarct scintigraphy: Technetium-99m pyrophosphate scintigrams were abnormal in 17 (89 percent) of the 19 patients who had undergone myocardial infarct scintigraphy during their admission for acute myocardial infarction. The two normal scintigrams were obtained from patients studied 4 and 6 days, respectively, after an initial subendocardial myocardial infarction. On the basis of separation of patients into two groups, those with anterior, anteroseptal or anterolateral infarction and those with inferior, inferoposterior or inferolateral infarction, the site of infarction as determined from the initial electrocardiograms, initial technetium-99m pyrophosphate images, follow-up thallium images and follow-up radionuclide ventriculograms corresponded in all cases.

Discussion

Thallium-201 Imaging

Our results indicate that focal myocardial scars persist and are detectable with thallium-201 scintigraphy late after myocardial infarction among patients with a wide range of infarct size, type (transmural or subendocardial) and location (anterior or inferior). Thallium-201 imaging detects areas of relatively decreased myocardial perfusion[17] that do not necessarily reflect irreversible injury. However, defects on thallium-201 images at rest do correlate in size with the pathologic extent of myocardial infarction[2] and, because our patients were studied at rest and in the absence of chest pain or electrocardiographic evidence of recurrent ischemia, these defects most likely reflected completed infarction.[18–21] Although detection of prior myocardial infarction with thallium-201 scintigraphy may exhibit a threshold phenomenon, abnormal results were frequently obtained even in patients with a small infarct (less than 20 CK-g-eq). Thus, substantial myocardial infarction of major clinical importance, sufficient to elicit impaired left ventricular dysfunction or late congestive heart failure, should always be detectable, except perhaps in the very rare situation of uniform global myocardial damage. Because all of the patients were studied more than 6 months after myocardial infarction, at a time when scar formation would be virtually complete, the perfusion defects that were detected should persist indefinitely.

Comparison with previous studies: Wackers et al.[1] performed thallium-201 imaging in patients 24 to 48 hours after acute myocardial infarction and observed an overall frequency of abnormal scans of 90 percent (including those interpreted as "positive" or "questionable"). Their study did not include a control group. Most of the patients studied (71 percent) had transmural myocardial infarction, but even among patients considered least likely to show positive results—those with a small infarct (peak serum glutamic oxaloacetic transaminase less than 3.5 times the upper limit of normal) and those undergoing scanning more than 48 hours after infarction—79 percent had an abnormal scan.

Recently Niess et al.[22] reported an overall sensitivity of 75 percent for thallium-201 imaging in detecting prior myocardial infarction. However, their study was re-

trospective, elevation of MB creatine kinase was not required to document myocardial infarction, and estimates of infarct size were not available. Nevertheless, 95 percent of patients with electrocardiographic evidence of prior myocardial infarction exhibited defects on thallium-201 images.

Radionuclide Ventriculography

Abnormal radionuclide ventriculograms were less frequent in this study than were abnormal thallium-201 scans, especially among patients with an infarct size less than 20 CK-g-eq. Nonetheless, persistent regional wall motion abnormalities were identified late after myocardial infarction in approximately 75 percent of patients. The site of abnormality determined by this method corresponded to the site of defects in thallium-201 scans, as well as to the site of technetium-99m pyrophosphate uptake and electrocardiographic abnormalities present at the time of the index infarction.

Correlation of infarct size and location and left ventricular function: In the study of Niess et al.,[22] regional wall motion abnormalities were noted at cardiac catheterization in all patients studied who had electrocardiographic evidence of transmural myocardial infarction but in only 84 percent of the entire group catheterized. Although radionuclide ventriculography is a less sensitive modality than thallium scintigraphy for detecting prior myocardial infarction, especially for small and inferior infarctions, it provides additional information characterizing left ventricular function. The results of both first pass and multigated radionuclide ventriculograms correlate well with clinical status and prognosis,[7,23] with left ventricular function assessed echocardiographically[24] and with left ventricular ejection fraction determined with contrast ventriculography.[16,25] In our study the weak correlation between the initial estimate of infarct size and radionuclide ejection fraction, determined much later, is not surprising because the extent of occult underlying myocardial disease may lead to relatively extensive depression of ejection fraction, or a particularly favorable distribution of infarction may result in relative preservation of ejection fraction compared with that based on consideration of extent of infarction alone.[26] In this study, we did not assess right ventricular function, which is frequently abnormal in patients with inferior infarction. In some of these patients, only right ventricular function may be impaired, and it is thus possible that evaluation of right ventricular ejection fraction and regional wall motion might improve the sensitivity of radionuclide ventriculography for detection of prior inferior infarction.

Electrocardiography

The electrocardiogram is a relatively insensitive index of old myocardial infarction.[27,28] Subendocardial myocardial infarction often cannot be documented at all late after an episode, Q waves may resolve after a transmural event, Q waves on the inferior leads may be equivocal, or conduction disturbances may mask electrocardiographic criteria of infarction. Specificity is also a problem[28] because chronic obstructive pulmonary disease, ventricular hypertrophy or conduction disturbances may give rise to Q waves in the absence of infarction. The frequency of positive results with both thallium scintigraphy and radionuclide ventriculography in our study was significantly greater than that with the electrocardiogram in patients with prior myocardial infarction (Table I). Nevertheless, the site of myocardial infarction, when evident electrocardiographically, correlated with the location of perfusion defects as has been noted by other investigators.[2,6,22]

Implications

Both thallium-201 scintigrams and radionuclide ventriculograms are frequently positive among patients with prior myocardial infarction. The magnitude of interobserver variability in interpretation of both the thallium-201 images and the radionuclide ventriculograms in our study is similar to that reported by earlier investigators.[29,30] This degree of variability should not seriously hamper the utility of these techniques for detection of remote myocardial infarction. Scintigraphically detectable perfusion defects persist for at least 6 months and, presumably, indefinitely. The sites of thallium defects and of regional wall motion abnormalities correspond closely and are concordant with electrocardiographic and technetium-99m pyrophosphate sites of antecedent acute myocardial infarction. Radionuclide ventriculography provides additional information characterizing late left ventricular function. Thus, these nuclear medicine techniques should be helpful in identifying and localizing prior myocardial infarction, particularly among patients with intraventricular conduction abnormalities or equivocal electrocardiographic findings.

Acknowledgment

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Left Ventricular Function in Mitral Valve Prolapse: Assessment With Radionuclide Cineangiography

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Abnormalities of left ventricular contraction in patients with mitral valve prolapse have suggested a myocardial factor in this disease. To determine systolic left ventricular function in mitral valve prolapse, technetium-99m gated equilibrium radionuclide cineangiography was performed in 47 patients with this diagnosis. In 39 patients without mitral regurgitation the average ejection fraction was normal at rest (average [± standard error of the mean] 57 ± 3 percent, normal 57 ± 1 percent, difference not significant) and exceeded the lower limits of normal in all but 1 patient, whose ejection fraction was 41 percent. However, ejection fraction during maximal exercise was lower for the group of patients with mitral prolapse without mitral regurgitation than for normal subjects (average 64 ± 2 percent, normal 71 ± 2 percent, $p<0.005$). In eight patients with mitral prolapse and mitral regurgitation, the average ejection fraction was normal at rest but was diminished with exercise in comparison with both normal subjects and patients with mitral valve prolapse without mitral regurgitation. Chest pain, arrhythmia and the pattern or extent of mitral valve prolapse on echocardiography were not independently associated with impaired left ventricular functional reserve. We conclude that, although many patients with mitral valve prolapse have normal left ventricular function, there is a subgroup without mitral regurgitation in whom diminished left ventricular functional reserve is suggestive of a cardiomyopathic process.

The presence of left ventricular contraction abnormalities,[1,2] chest pain and ventricular arrhythmia in patients with mitral valve prolapse suggested a myocardial component in this condition. In addition, symptoms and electrocardiographic abnormalities associated with mitral valve prolapse may not be easily distinguished from those of coronary artery disease. Because it has recently become evident that mitral valve prolapse is a relatively common disorder, occurring in 5 to 10 percent of our population,[3–5] it is of practical importance to determine the functional derangements associated with this condition and to define a reliable noninvasive means of excluding hemodynamically important coronary arterial obstruction in those patients with mitral valve prolapse and symptoms suggestive of ischemia.

In this study, we employed radionuclide cineangiography in patients with mitral valve prolapse to assess systolic left ventricular performance at rest and during exercise, independent of coexisting coronary artery disease. The results of this functional assessment were correlated with the clinical, echocardiographic and electrocardiographic findings in patients with this condition.

Methods

Study patients: Patients with mitral valve prolapse seen at the National Heart, Lung, and Blood Institute between May 1978 and February 1979 were studied. The group consisted of 33 women and 14 men, aged 15 to 65 years (mean 39). Of these 47 patients, 39 (10 men and 29 women with a mean age of 39 years) did not have clinically important mitral regurgitation, as determined from the physical examination, absence of left atrial or left ventricular enlargement on

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echocardiography and, in 10 patients, the findings on left ventricular contrast angiography. Eight patients did have moderate or severe mitral regurgitation confirmed angiographically. Coronary angiography was performed in 10 patients.

The presence of mitral valve prolapse was determined by the finding of a midsystolic click on auscultation, with or without the presence of a late systolic murmur. The criteria for mitral valve prolapse on echocardiography were applied as described elsewhere.[6] A patient was judged to have mitral valve prolapse if either echocardiographic or auscultatory criteria were present. Of 39 patients without clinically important mitral regurgitation, 30 had a mid systolic click at the time of study. Of nine patients without a click, seven had a late systolic apical murmur. The two patients without auscultatory evidence of mitral prolapse each had a markedly positive mitral valve echogram, with late systolic posterior displacement of the mitral valve from the C-D line exceeding 5 mm. In all patients administration of cardiac medications was discontinued at least 72 hours before study.

Echocardiographic techniques: Echocardiograms were performed with a 2.25 megahertz, 1.25 cm diameter unfocused transducer connected to a commercially available ultrasonograph and strip chart recorder. Each patient was studied in the basal state in a supine position. Care was taken to record both mitral valve leaflets with the transducer held perpendicular to the chest wall, usually at the fourth or fifth left intercostal space.[7] To prevent a false pattern of mitral valve prolapse, caudal angulation of the transducer was avoided.[8] End-diastolic left ventricular dimensions were measured as the maximal distance between the left side of the interventricular septum and endocardium of the posterior free wall[9] with the ultrasonic beam passing through the left ventricle at or slightly caudal to the tips of the mitral leaflets.

Electrocardiograms: Standard 12 lead electrocardiograms were obtained in each patient. Ambulatory 24 hour electrocardiographic records on magnetic tape were obtained in 37 patients during normal activity. The playback was displayed in real time on a large screen oscilloscope (Clinical Data Inc., Boston, Massachusetts) for visual identification of ectopic beats and other arrhythmias, which were subsequently tabulated by computer. Ventricular arrhythmia was graded according to a system similar to that discribed by Lown et al.[10] The following categories were used:

Grade 0: no ventricular premature depolarizations in 24 hours.

Grade 1: occasional ventricular premature depolarizations; no more than 30 in any hour of monitoring.

Grade 2: more than 30 ventricular premature depolarizations in any hour of monitoring or more than 1 such depolarization in 2 minutes of exercise testing.

Grade 3: multiform ventricular premature depolarizations.

Grade 4a: ventricular couplets (two consecutive ventricular premature depolarizations).

Grade 4b: ventricular tachycardia, that is three or more consecutive ventricular premature depolarizations in succession.

Exercise testing: Upright bicycle ergometry was performed using a modified CM_5 system, including a V_5 lead for detection of abnormalities with an anterior vector and a sacral lead for detection of abnormalities with an inferior vector. Exercise was continued until the development of chest pain or limiting fatigue. The exercise electrocardiogram was assessed for the presence of arrhythmias and repolarization abnormality; S-T segment depression with a flat or negative slope of 0.1 mV for 80 ms or more in either monitored lead was considered a positive response.

Radionuclide cineangiography: Radionuclide cineangiography was performed with the subjects in a supine position at rest and during maximal symptom-limited supine bicycle exercise.[11] In vivo labeling of red blood cells with 10 to 15 millicuries of technetium-99m was effected by injecting the isotope 30 minutes after the intravenous administration of stannous pyrophosphate. This dose of technetium coupled with a high sensitivity collimator results in 20,000 events/s in a 15 by 15 cm field of view surrounding the heart. Background radiation was determined by creating a crescent of pixels located 1 pixel width outside the lateral border of the region of interest. After equilibration of the tracer in the blood pool, a Anger camera was oriented in the modified left anterior oblique position to isolate the left ventricle in the field of view.[12] Angulation of the camera 15° toward the feet, that the camera is approximately perpendicular to the long axis of the left ventricle, helps to exclude the left atrium from the left ventricular area of interest. Imaging was performed with the use of a computer-based procedure gated to the electrocardiogram, as described elsewhere.[13] To further exclude contribution of atrial activity to the left ventricle, only the difference image is used to draw the left ventricular area of interest at the level of the valve plane. Hence, if there were an area of overlap of the left ventricle and left atrium, exclusion of counts from the overlying left atrium, as well as from a small portion of the base of the left ventricle, would occur in systole and diastole. This technique, while excluding left atrial contamination, causes negligible error in the determination of global left ventricular ejection fraction. Left ventricular ejection fraction could then be determined by computer-assisted analysis of left ventricle time-activity curves.[13] Excellent correspondence ($r \pm 0.92$, $p < 0.001$) of radionuclide ejection fractions with those obtained with contrast angiography has been previously established.[14]

After images were obtained at rest, supine bicycle exercise was begun with 25 watt increments in the exercise load at 3 minute intervals. Exercise was continued until limitation by severe fatigue, chest pain or severe dyspnea. Imaging was begun when the patient indicated moderate fatigue, and continued until the symptom-limited end point. In all subjects, heart rate and blood pressure (measured using arm cuff sphygmomanometry) were recorded at 1 to 2 minute intervals during exercise. After completion of imaging the portion of the image sequence corresponding to maximal exercise was selected for analysis.[13] Each patient underwent continuous imaging throughout most of the exercise period, beginning with mild to moderate exercise, and continuing through the termination of exercise. Beat length windowing (list mode data acquisition) was employed to permit selection of that portion of the imaging sequence corresponding to maximal exercise, always including the last 1.5 to 2 minutes of exercise. Regional wall motion was determined visually by two independent observers directly from the cine display. Whereas assessment of the anteroseptal and anterolateral ventricular walls was made directly from the latter, functional evaluation of regions of myocardium not contributing to the edges of the cardiac silhouette in the modified left anterior oblique position was performed from difference images created by subtracting the end-systolic from the end-diastolic image.

Ejection fractions obtained at rest and during exercise were compared with those previously determined in 30 normal subjects.[13,14] The normal subjects ranged in age from 19 to 63 years and had no clinical, echocardiographic or electrocardiographic evidence of cardiovascular disease. Nine of these normal subjects were women and 21 were men.

Statistical comparisons were made using Student's *t* test. Data were expressed as the average ± standard error of the mean.

Results

Mitral Valve Prolapse Without Mitral Regurgitation

Radionuclide cineangiography: Ejection fraction at rest in 39 patients without mitral regurgitation (Fig. 1) averaged 57 ± 3 percent compared with 57 ± 1 percent for normal subjects (difference not significant [NS]) and equaled or exceeded the lower limits of normal (45 percent) in all but 1 patient. In this patient the ejection fraction at rest was 41 percent. In contrast, ejection fraction during maximal exercise was 64 ± 2 percent, compared with 71 ± 2 percent for normal subjects ($p < 0.005$) and was below the lower limits of normal, that is, 58 percent during maximal exercise,[14] in nine (23 percent) patients. Of these nine patients, five who achieved a heart rate of 113 to 178 beats/min (mean 144) during maximal exercise had an ejection fraction during maximal exercise that was marginally depressed (55 to 57 percent). Values as low as 54 percent have been recorded during submaximal exercise (heart rate 105 to 120 beats/min) in normal subjects.[13] Because the number of normal subjects studied was relatively small, the significance of a borderline low ejection fraction during maximal exercise in these five patients with mitral valve prolapse is uncertain. However, in four patients, who also achieved an appropriate response of heart rate to maximal exercise, the ejection fraction during maximal exercise was substantially decreased (less than 54 percent) to levels below those noted in any normal subject even during mild exercise. Hence, these four persons with mitral prolapse probably did manifest diminished left ventricular functional reserve.

Ejection fraction was distinctly abnormal in two patients, one of whom showed a marked decline in ejection fraction from an initially normal value of 69 percent at rest to a clearly abnormal value of 47 percent during exercise. In the other patient, an initially low ejection fraction at rest of 41 percent showed no increase with exercise. All normal subjects showed an increase in ejection fraction with exercise.

Role of heart rate and blood pressure: Although marked differences in heart rate may influence ejection fraction,[14] the heart rates (average 75 ± 2 beats/min at rest, 136 ± 3 beats/min during exercise) of the patients with mitral valve prolapse did not differ importantly from average heart rates at rest (66 ± 2 beats/min) and during exercise (143 ± 3 beats/min) of the normal subjects. The average systolic blood pressure at rest (122 ± 4 mm Hg) was higher than that in normal subjects (114 ± 2 mm Hg, $p < 0.01$). With exercise, systolic blood pressure in patients with mitral valve prolapse (171 ± 5 mm Hg) was somewhat lower than that of the normal subjects (189 ± 4 mm Hg). However, comparison of the patients with mitral prolapse (predominantly female) with normal women shows no significant differences in heart rate at rest (average 71 ± 3 beats/min) or during exercise (average 149 ± 4 beats/min), and systolic blood pressure during exercise (178 ± 5 mm Hg). In the patient whose low ejection fraction at rest of 41 percent failed to increase with exercise, heart rate increased from 71 beats/min at rest to 120 beats/min with exercise, accompanied by an increase in systolic blood pressure from 140 mm Hg at rest to 190 mm Hg with exercise. Another patient with an ejection fraction of 54 percent at rest and only 55 percent with exercise manifested a heart rate of 76 beats/min at rest and 135 beats/min with exercise. Systolic blood pressure increased from 145 to 220 mm Hg.

Role of coronary artery disease: In the two patients with an abnormal response of ejection fraction to exercise, coronary angiography failed to disclose coronary arterial abnormality. Regional wall motion abnormality at rest or with exercise was not observed in any patient with mitral valve prolapse.

To exclude the possible influence of occult coronary arterial stenosis, a separate assessment of left ventricular function was performed in 20 of the 39 patients without mitral regurgitation. This subgroup contained 10 patients with normal coronary arteriograms and 10 patients who did not have coronary arteriography but were unlikely to have coronary artery disease because they were women under 40 years of age (Fig. 2). Even in this subgroup, ejection fraction with exercise was significantly lower in patients with mitral valve prolapse than in normal subjects. Furthermore, three patients with prolapse and a normal coronary arteriogram, including one patient with an abnormal ejection fraction at rest, had a subnormal ejection fraction during exercise.

Clinical features: Chest pain was noted in 21 (54 percent) and palpitations were reported in 20 (51 percent) of the 39 patients with mitral valve prolapse and no mitral regurgitation. However, among the 31 patients who underwent 24 hour electrocardiographic monitor-

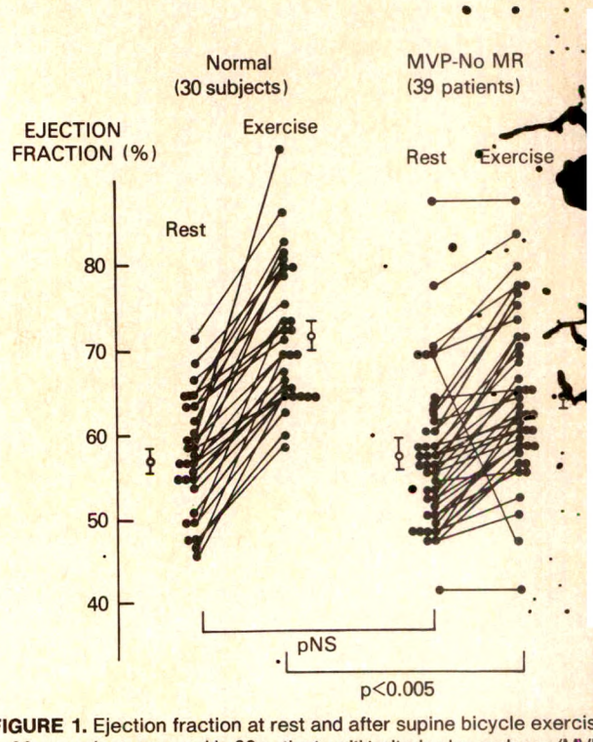

FIGURE 1. Ejection fraction at rest and after supine bicycle exercise in 30 normal persons and in 39 patients with mitral valve prolapse (MVP) but no mitral regurgitation (MR). See text for discussion. NS = not significant; p = probability.

ing, there was no difference in ejection fraction at rest or during exercise in patients with and without chest pain. Nine of the 31 patients had Lown grade 2 through 4b ventricular arrhythmia and 22 had grade 0 or grade 1 ventricular arrhythmia. Although the former group had a slightly lower ejection fraction with exercise (Fig. 3) than the latter, this difference was not statistically significant (61 ± 5 versus 64 ± 2 percent). Three patients had 0.1 mV S-T segment depression during maximal upright bicycle exercise. One of these three patients evidenced decreased left ventricular functional reserve, with ejection fraction decreasing from 69 percent at rest to 47 percent during exercise.

Echocardiography: Echocardiograms were sufficient for evaluation in 36 of 39 patients. Late systolic prolapse was apparent in 21 patients (58 percent) and holosystolic prolapse in 10 patients (28 percent). Five subjects had echocardiograms that were not diagnostic of mitral prolapse. The diagnosis in these patients was determined by the auscultatory finding of a mid systolic click with or without a late systolic murmur. Posterior displacement of the C-D line in the mitral valve echogram exceeded 5 mm in 12 patients (average 7 mm) and was 4 mm or less in 24 patients (average 3 mm, $p < 0.001$). There was no significant difference in ejection fraction between these two groups (Fig. 4) at rest or with exercise (60 ± 3 percent in patients with 5 mm or greater C-D displacement, 66 ± 2 percent in patients with 4 mm or less). There was also no relation between left ventricular function and the pattern of mitral valve prolapse on echocardiogram. Left atrial dimension was normal in all patients, including those with left ventricular dysfunction.

Mitral Prolapse and Mitral Regurgitation

The eight patients with mitral valve prolapse and moderate to severe mitral regurgitation had an ejection fraction at rest of 56 ± 3 percent and did not differ significantly from normal subjects or from patients with mitral valve prolapse without mitral regurgitation (Fig. 5). However, left ventricular functional reserve for this group was diminished compared with that in patients without mitral regurgitation, as evidenced by a subnormal average ejection fraction during exercise of 53 ± 4 percent compared with 64 ± 2 percent in patients without mitral regurgitation ($p < 0.01$). Subnormal ejection fraction during maximal exercise has also been noted in patients with mitral regurgitation from causes other than mitral prolapse.[15] Four of the five patients with mitral prolapse and mitral regurgitation whose ejection fraction decreased during exercise (Fig. 5) had left ventricular end-diastolic dimensions on echocardiography greater than 66 mm. However, the small number of patients does not permit a statistically valid evaluation of the relation between left ventricular diastolic dimensions and left ventricular function.

Discussion

Although myxomatous degeneration of the mitral valve is the principal abnormality in mitral valve prolapse, the presence of "ischemic" electrodiographic changes,[16,17] chest pain,[18,19] arrhythmias[20] and the occasional occurrence of sudden death not due to severe mitral regurgitation and congestive heart failure[18,21,22] suggest the coexistence of a primary myocardial abnormality. Hemodynamic studies demonstrating that

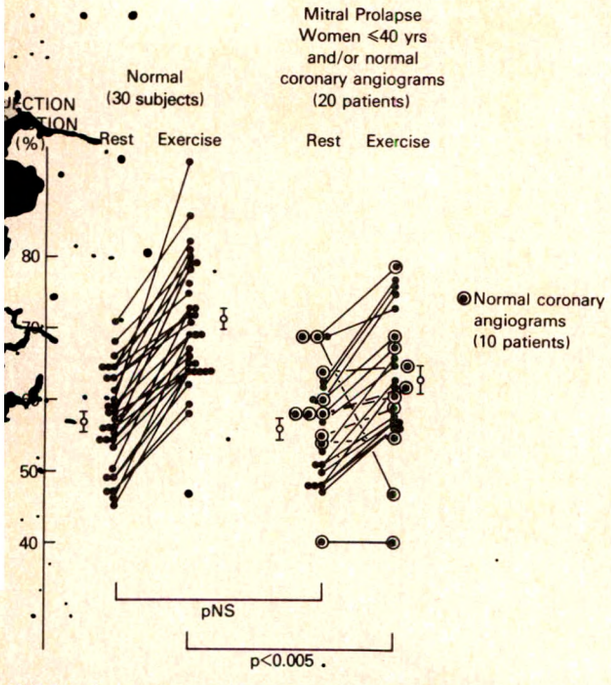

FIGURE 2. Comparison of ejection fraction at rest and with exercise in 30 normal subjects and 20 patients with mitral valve prolapse and normal coronary arteriograms or women less than 40 years of age. The two patients with clearly abnormal left ventricular function both had normal coronary arteriograms.

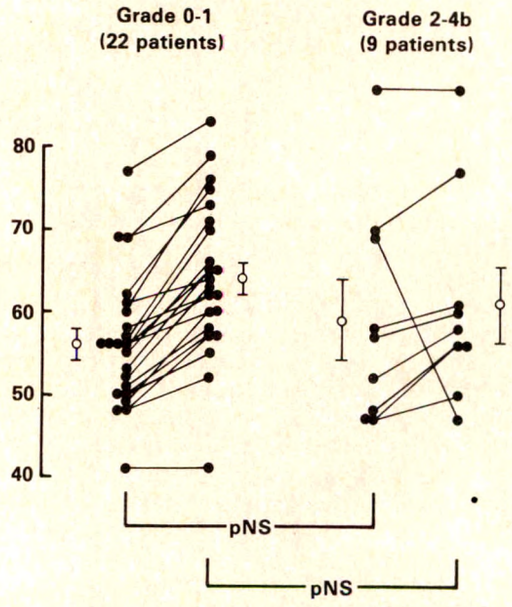

FIGURE 3. Systolic left ventricular function at rest and with exercise in patients with no or minimal (grade 1) ventricular arrhythmia compared with those patients with more severe grades (2–4b) of arrhythmia. No significant differences between groups are noted.

some patients have elevated left ventricular end-diastolic pressure, decreased cardiac index at rest, failure of the cardiac index to increase appropriately with exercise, and abnormalities of left ventricular wall motion[1,2,23] also suggest a myocardial component, as does the finding of myocardial histologic abnormalities on transvenous endomyocardial biopsy.[24]

Our findings demonstrate that abnormalities in left ventricular function occur in patients with mitral valve prolapse and mitral regurgitation. However, decreased left ventricular functional reserve has also been noted in patients with mitral regurgitation from causes other than mitral prolapse,[15] probably reflecting the effects of chronic volume overload. Hence, the interpretation of such a finding in patients with mitral prolapse and regurgitation is ambiguous. More convincingly, ejection fraction during exercise was below the limits of normal, or declined from values at rest, in several patients with mitral prolapse who did *not* manifest clinically apparent mitral regurgitation. Moreover, the mean ejection fraction during exercise for this group, or for the patients with mitral valve prolapse without mitral regurgitation *and* with no or little likelihood of coronary disease, was lower than that of normal subjects.

Mechanism of myocardial dysfunction in mitral prolapse: Although these abnormalities suggest that a primary aberration of myocardial function exists in some patients with mitral valve prolapse, alternative explanations are possible. For example, in our patients who had no evidence of mitral regurgitation at rest, mitral regurgitation could have developed during exercise and could conceivably have been responsible for the abnormal left ventricular function observed during exercise. However, although patients with chronic mitral regurgitation may evidence abnormal left ventricular reserve as indicated by a decrease in ejection fraction during exercise, acute mitral insufficiency developing during exercise in those patients with mitral valve prolapse who do not have mitral regurgitation at rest would be expected to provide a low impedance runoff for the left ventricle. Hence, an increase in ejection fraction during exercise, rather than the observed decrease, would be likely.

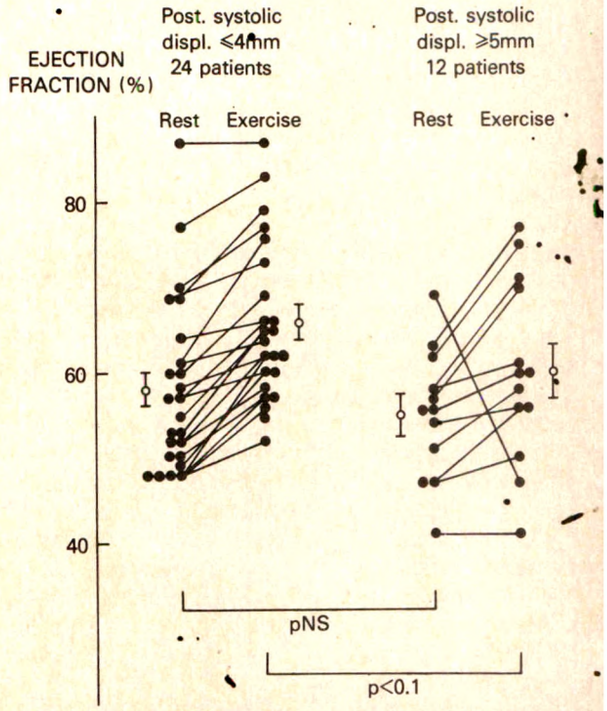

FIGURE 4. Left ventricular systolic function at rest and with exercise categorized according to extent of mitral prolapse estimated from M mode echocardiogram. Differences noted do not achieve statistical significance. displ. = displacement; Post. = posterior.

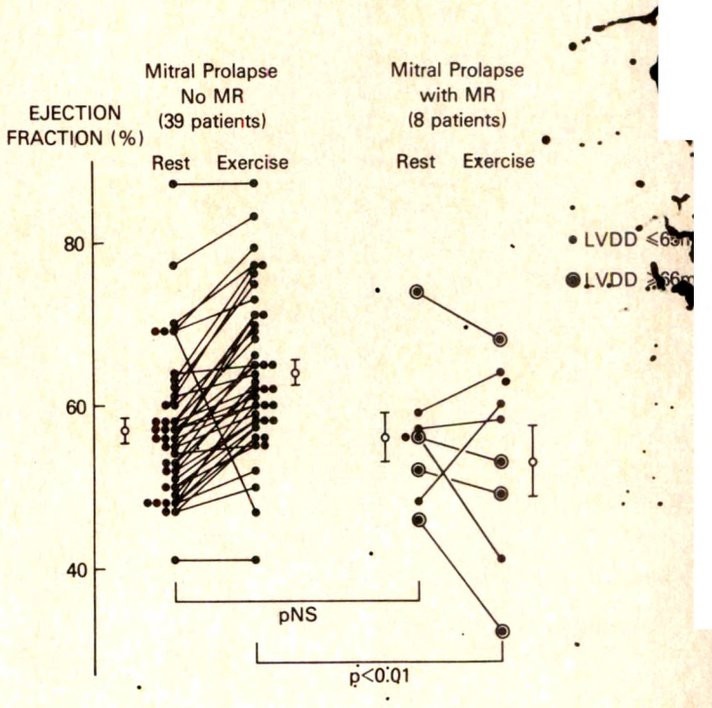

FIGURE 5. Comparison of left ventricular ejection fraction in those patients with mitral valve prolapse with (n = 39) and without (n = 8) concomitant mitral regurgitation (MR). Although ejection fraction in the two groups is the same at rest, it is significantly lower with exercise in patients with than in those without mitral regurgitation. LVDD = left ventricular end-diastolic diameter in echocardiogram.

In criticism of other results suggesting a "myocardial" theory of mitral valve prolapse, Jeresaty[25] noted the confusing heterogeneity of left ventricular wall motion abnormalities that have been described, and thought that some of these abnormalities might have been factitious. Even if regional wall motion abnormalities did exist, he suggested that fibrosis of papillary muscles and regions of adjacent myocardium, consequent to traction from mitral leaflet "sail forces," might explain hypokinesia or akinesia. The disappearance of left ventricular contraction abnormalities in patients with mitral valve prolapse after mitral valve replacement[26] supports this "valvular" theory of mitral prolapse, at least for the abnormalities seen in some patients. However, these considerations do not account for the decrease in global left ventricular functional reserve and absence of regional wall motion abnormality noted in our patients. Moreover, if abnormalities in left ventricular function and the occurrence of chest pain and arrhythmias were secondary to the effects of mitral valve prolapse on the papillary muscles and their myocardial attachments, one might expect the presence of left ventricular dysfunction to be related to the severity of prolapse. However, neither the extent nor the pattern of mitral prolapse assessed with echocardiography correlated with the presence of chest pain, the extent of rhythm abnormality or the development of abnormal left ventricular function during exercise.

Myocardial perfusion abnormalities represent another potential cause of abnormal left ventricular function in patients with mitral valve prolapse. Preliminary communications[27,28] have suggested the presence of myocardial perfusion defects on thallium scan at rest as well as during exercise in patients with mitral valve prolapse; however, Klein et al.[29] found normal myocardial perfusion during exercise stress in all 22 patients studied who had normal coronary arteriograms, despite the presence of chest pain or positive echocardiographic exercise stress tests in many. The latter results have been independently confirmed by others.[30,31]

Clinical implications: Of practical importance to the management of patients who have a disease with symptoms simulating coronary artery disease is the development of a noninvasive means of distinguishing those patients with mitral prolapse and coincidential coronary artery disease from those patients with mitral valve prolapse and normal coronary arteries. Only a small subgroup of our patients with mitral valve prolapse had an abnormal ejection fraction response to exercise and no patient in the present series evidenced regional left ventricular dysfunction, abnormalities usually found in patients with coronary artery disease.[11] It may therefore be inferred that the absence of these abnormalities on radionuclide cineangiography in a patient with mitral prolapse excludes with high probability the presence of coexisting significant coronary artery disease. The converse, however, is less certain. Abnormal global left ventricular function may be present in patients with mitral prolapse in the absence of coronary artery disease. Also, while none of our patients evidenced asynchronous left ventricular wall motion on radionuclide cineangiography, this finding by other investigators[1,2] using contrast left ventriculography suggests that the presence of regional contraction abnormalities may not unequivocally denote underlying coronary disease in patients with mitral valve prolapse.

Acknowledgment

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Cardiac Function During Rest and Exercise in Patients With Mitral Valve Prolapse

Role of Radionuclear Angiocardiography

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The clinical features of mitral valve prolapse syndrome and ischemic coronary disease overlap, making differentiation of the two conditions difficult. Furthermore, many patients have both conditions. This study assessed changes in ventricular function during rest and exercise in patients with mitral valve prolapse alone and in patients with prolapse and concomitant coronary artery disease. Twelve patients with angiographically documented mitral valve prolapse and normal coronary anatomy and 11 patients with normal coronary anatomy and no mitral valve prolapse had increased ejection fraction and demonstrated no wall motion abnormality during exercise. Changes in ventricular function during exercise in 11 additional patients with mitral valve prolapse demonstrated on echocardiography were similar to those in the group with mitral valve prolapse and normal coronary anatomy seen on angiography. In contrast, 6 of 11 patients with mitral valve prolapse and coronary arterial stenosis demonstrated on angiography had a decreased ejection fraction and exhibited wall motion abnormalities during exercise. These results suggest that mitral valve prolapse alone has no detrimental effect on ventricular function during rest and exercise and that exercise-induced abnormalities in ventricular function are related to the presence and severity of coronary artery disease and not to mitral valve prolapse.

Prolapse of the mitral valve is a common but usually innocuous disorder. The clinical features of this syndrome frequently mimic those of ischemic heart disease[1,2] and its diagnosis is further complicated by the relatively common coexistence of coronary artery disease.[3,4] In addition, mitral valve prolapse in patients with normal coronary arteries has been suggested as one potential cause of myocardial ischemia. Because of these considerations, patients with mitral valve prolapse commonly come to cardiac catheterization. Noninvasive diagnostic techniques have been developed that hold the potential for assessing both prolapse of the mitral valve and myocardial ischemia. Measurement of left ventricular function during rest and exercise with radionuclide angiocardiography appears to be a sensitive technique for recognition of coronary artery disease, and patients with myocardial ischemia typically exhibit a decrease in ejection fraction and new wall motion abnormalities during exercise.[5,6] Left ventricular function during rest and exercise has not been evaluated in patients with mitral valve prolapse. The purpose of this investigation was to assess whether prolapse of the mitral valve without concomitant coronary artery disease can cause cardiac functional alterations during exercise and whether patients with both mitral valve prolapse and coronary artery disease can be separated from patients with the former disorder alone.

Methods

Patients: Radionuclide angiocardiography during rest and exercise has been performed as a clinical study at Duke University Medical Center since April 1977. Since then, 455 patients underwent both cardiac catheterization for evaluation of chest pain and radionuclide angiocardiography during rest and exercise. In

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the same period, 296 patients underwent echocardiography and radionuclide angiocardiography during rest and exercise but did not undergo cardiac catheterization. Retrospective analysis of these patients by retrieval of data from a computerized information system identified four homogeneous groups for this study.[7] Group I consisted of persons documented to have a totally normal cardiovascular system except for a history of chest pain. Group II comprised patients with normal coronary arteriograms and definite mitral valve prolapse documented during contrast left ventriculography. Group III consisted of patients with a 75 percent or greater reduction in the diameter of at least one major coronary artery on coronary angiography and definite mitral valve prolapse on left ventriculography. Group IV was defined as patients with definite mitral valve prolapse demonstrated on echocardiography; patients in this group did not undergo cardiac catherization.

Group I: The 11 normal patients (4 women, 7 men) in this group had a mean age (± standard error of the mean) of 48 ± 8 years (range 35 to 58). Five patients presented with nonanginal chest pain, five with atypical angina and one with a history of typical angina. No patient had a history of hypertension, myocardial infarction or prior positive exercise treadmill test. Nine patients had a normal electrocardiogram, and two had nonspecific ST-T wave changes. All 11 patients underwent complete cardiac catheterization and had normal hemodynamic measurements, completely normal coronary arteriogram without even minor irregularities, normal left ventricular function with a resting ejection fraction greater than 0.50 and no mitral valve prolapse. In addition, no patient was taking medication with known cardiac effects near the time of radionuclide angiocardiography.

Group II: This group consisted of 12 patients, 8 women and 4 men, with mitral valve prolapse but no coronary artery disease demonstrated at cardiac catheterization. Their mean age was 49 ± 10 years (range 35 to 62). Seven had been evaluated for chest pain atypical of angina, three for typical chest pain and one because of a previous positive exercise treadmill test. Of the 10 patients presenting with chest pain, 7 had previously been hospitalized one or more times for severe chest pain, but no myocardial infarction had been documented with serial electrocardiograms or cardiac enzyme assay. Eight of the 12 patients had either a systolic click or a midsystolic murmur. Four had nonspecific ST-T wave changes, and eight a normal electrocardiogram. Three of the eight patients who underwent treadmill testing had a positive exercise treadmill examination immediately before cardiac catheterization. Cardiac catheterization in this group documented definite mitral valve prolapse but normal hemodynamic findings and coronary arteries. Left ventriculography revealed a trace of mitral regurgitation in three patients and no mitral regurgitation in nine. The 12 patients appeared to have a normal cardiovascular system except for prolapse of the mitral valve documented angiographically.

Group III: This group consisted of 11 patients, 4 women and 7 men, with mitral valve prolapse associated with coronary artery disease. Their mean age was 48 ± 5 years (range 38 to 54). All 11 patients had chest pain that was considered typical of angina in 8 and atypical of angina in 3. Six patients had previously been hospitalized one or more times for severe pain, but myocardial infarction was not documented. Four patients had either a systolic click or a mid systolic murmur. Eight had a normal electrocardiogram, and three had nonspecific ST-T wave changes. Of nine patients undergoing exercise treadmill testing, five had positive results, three indeterminate results and one a negative result. Cardiac catheterization confirmed prolapse of one or both cusps of the mitral valve in all patients, and three had a trace of mitral regurgitation seen on left ventriculography. Coronary arteriograms demonstrated lesions obstructing at least 75 percent of the vessel diameter in all patients, and these lesions were present in one major coronary artery in three patients, two major coronary arteries in four and all three major coronary vessels in four. These patients can be characterized as having documented coexistence of mitral valve prolapse and coronary artery disease.

Group IV: The 11 patients in Group IV, 7 women and 4 men, had mitral valve prolapse on echocardiography but no other demonstrable cardiac disease. These patients did not undergo cardiac catheterization so that the presence of coronary artery disease in this group could not be definitely excluded, but they did undergo radionuclide angiography. Their mean age was 39 ± 15 years (range 21 to 63). The five patients had presented with a history of atypical chest pain, four with palpitations and two with a previous positive exercise treadmill tests. No patient had had a prior myocardial infarction documented. Therefore, this group comprised patients with an echocardiographic diagnosis of mitral valve prolapse in whom the diagnosis of coronary artery disease did not appear likely but was not excluded by coronary arteriography.

Cardiac catheterization: All patients in Groups I, II and III underwent right and left heart catheterization that included right and left heart pressure measurements, collection of oxygen data, biplane left ventriculography and selective coronary arteriography. Mitral valve prolapse was diagnosed when one or both of the mitral leaflets was seen to move into the left atrium during systole in both the right anterior and left anterior oblique views.[8] The magnitude of mitral valve insufficiency was subjectively classified on a scale of 0 to 4 as determined by the rate of contrast clearance from the left atrium. Patients with 1+ or less mitral regurgitation were considered to have a trace amount of insufficiency, and all patients with a greater degree of insufficiency were excluded from the study. The data obtained during the evaluation of each patient undergoing cardiac catheterization were reviewed by three cardiologists and then entered into a computerized information system in a manner previously described.[7]

Echocardiography: Each of the patients in Group IV underwent two dimensional real time, phased array echocardiography. The two dimensional echographic appearance of the mitral valve leaflets, systolic mitral ring motion and adjacent left ventricular wall motion was analyzed. The presence of mitral valve prolapse was established using criteria described by Gilbert et al.,[9] and included: (1) posteriorly displaced coaptation of the leaflets during systole, (2) superior movement of one or both leaflets during systole above the level of the mitral anulus, and (3) systolic curling motion of the posterior mitral ring on adjacent myocardium.

Radionuclide angiocardiography: Each patient in the study underwent radionuclide angiocardiography at rest and during exercise by a standard protocol. The Baird System Seventy-Seven multicrystal computerized gamma camera was used to acquire and analyze the data obtained in the anterior projection with each patient seated on an isokinetic bicycle ergometer.[6,10] After acquisition of the data at rest, exercise was begun and a second radionuclide angiocardiogram was obtained when 85 percent of the maximal age-predicted heart rate (target heart rate) was achieved, or earlier if symptoms or electrocardiographic changes suggestive of ischemia precluded further exercise.

Variables measured with this technique from which the hemodynamic values were derived included left ventricular ejection fraction and end-diastolic volume. After background subtraction, the ejection fraction was determined from the change in counts from end-diastole to end-systole when peak radioactivity was within the left ventricle. Data recorded from several individual cardiac cycles permit construction of an

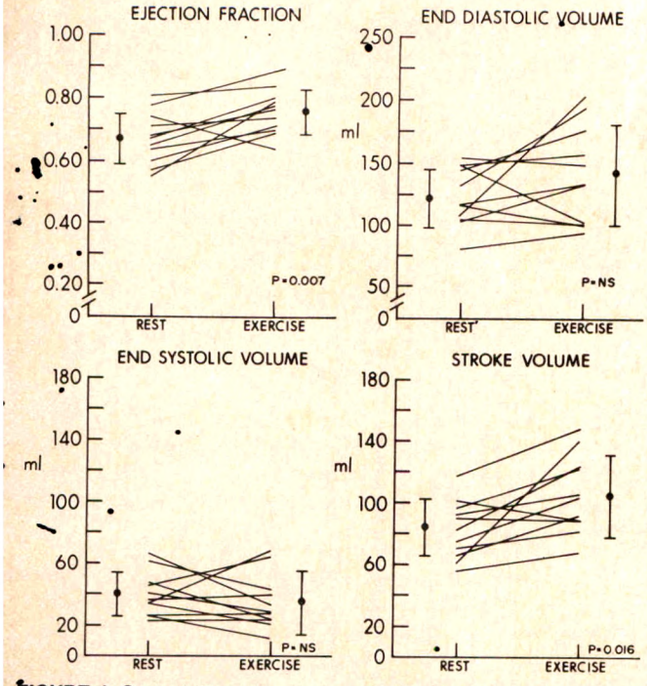

FIGURE 1. Group I. Response to exercise in 11 patients with normal coronary anatomy and no mitral valve prolapse. During exercise, the ejection fraction and stroke volume increased. NS = not significant; p = probability.

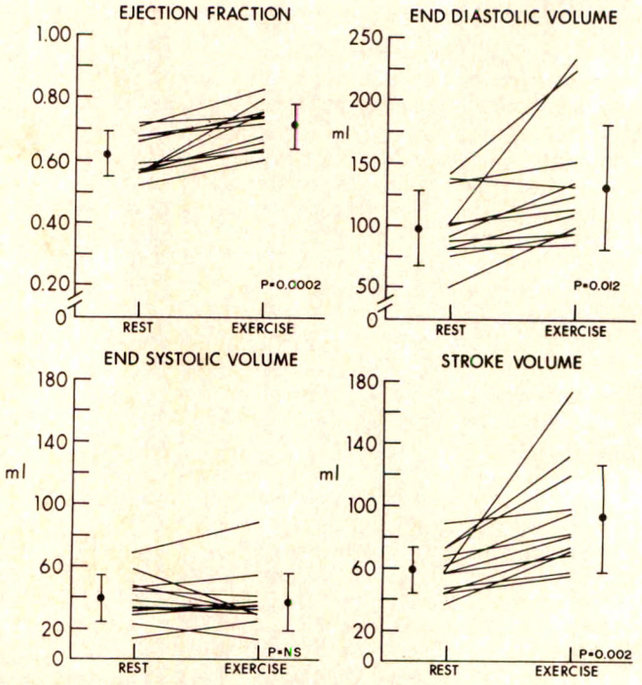

FIGURE 2. Group II. Effects of exercise in 12 patients with normal coronary anatomy and mitral valve prolapse. The ejection fraction, end-diastolic volume and stroke volume increased with exercise.

average or representative cardiac cycle. The images of the representative cardiac cycle are displayed in a static and cine format for assessment of wall motion. Planimetry of the perimeter and measurement of the major axis of the end-diastolic image of the left ventricle permitted end-diastolic volume determination with the formula of Dodge et al.[11] The stroke volume, end-systolic volume and cardiac output were derived from the ejection fraction and end-diastolic volume. Differences in left ventricular function during rest and exercise assessed with radionuclide angiocardiographic techniques were compared using the paired t test within the groups and the analysis of variance test between the groups. A probability (p) value of less than 0.05 was considered significant.

Results

Comparison of normal patients with patients with mitral valve prolapse: Each of the 11 normal patients (Group I) exercised to a heart rate beyond 85 percent of the age-predicted heart rate, and the average rate increased from 86 ± 17 beats/min at rest to 161 ± 17 beats/min during exercise. The mean blood pressure increased from 97 ± 11 mm Hg at rest to 111 ± 16 mm Hg during exercise. The average ejection fraction of the group increased (0.67 ± 0.08 to 0.76 ± 0.07), and only one patient had a decreased ejection fraction with exercise (Fig. 1). The end-diastolic volume increased (123 ± 24 to 140 ± 39 ml) and end-systolic volume decreased (40 ± 14 to 35 ± 20 ml during exercise. Exercise induced increases were documented in stroke volume (82 ± 19 to 105 ± 26 ml) and cardiac output (7.1 ± 2.4 to 16.8 ± 3.9 liters/min). There were no wall motion abnormalities during rest or exercise.

Changes in ventricular function during exercise in patients with mitral valve prolapse and normal coronary arteriograms (Group II) were similar to those in patients in Group I (Fig. 2). Eight of the 12 patients achieved or exceeded target heart rate during exercise, and the group change in rate from resting conditions to exercise was 89 ± 18 to 154 ± 14 beats/min. The mean blood pressure at rest was 100 ± 12 mm Hg and during exercise was 111 ± 16 mm Hg. Ejection fraction in-

TABLE I

Comparison of Groups I and II* by Analysis of Variance

	HR	BP	EF	EDV	ESV	SV	CO
Rest	NS	NS	NS	(I > II); p = 0.04	NS	(I > II); p = 0.006	(I > II); p = 0.02
Ex	NS	NS	NS	NS	NS	NS	NS

* Group I, patients with normal cardiovascular findings; Group II, patients with mitral valve prolapse and normal coronary angiograms.
BP = blood pressure; CO = cardiac output; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; Ex = exercise; NS = not significant; p = probability; SV = stroke volume.

creased with exercise in each patient, and the average increased from 0.61 ± 0.07 to 0.71 ± 0.07. The end-diastolic volume increased (99 ± 27 to 132 ± 49 ml) from rest to exercise; the end-systolic volume was unchanged (39 ± 15 versus 38 ± 19 ml). The stroke volume increased (60 ± 15 to 94 ± 35 ml), and the cardiac output increased (5.2 ± 1.1 to 14.4 ± 5.6 liters/min) during exercise. No patient in this group demonstrated wall motion abnormalities during rest or exercise.

The radionuclide angiocardiographic data of the patients with mitral valve prolapse and normal coronary anatomy (Group II) were compared with data in the patients without mitral valve prolapse and normal coronary anatomy (Group I) (Table I). Significant differences existed only during rest, and these differences were small and appeared to reflect the larger proportion of men in Group I. The end-diastolic volume, stroke volume and cardiac output during rest were greater in the group with normal coronary anatomy and no mitral valve prolapse. All differences disappeared during exercise, and patients with mitral valve prolapse had a response to exercise that could not be distinguished from that in the normal subjects.

Comparison of patients with mitral valve prolapse with and without coronary artery disease: The changes in ventricular function from rest to exercise in patients with coronary artery disease and mitral valve prolapse (Group III) differed from those in the other three groups (Fig. 3). Only 1 of the 11 patients achieved 85 percent of the age-predicted heart rate during exercise. This group had an average heart rate of 79 ± 18 beats/min at rest that increased to only 124 ± 22 beats/min during exercise. The average ejection fraction did not change from rest (0.60 ± 0.07) to exercise (0.58 ± 0.07), and 6 of the 11 patients had a decreased ejection fraction during exercise. The end-diastolic volume (114 ± 33 to 165 ± 44 ml), and end-systolic volume (47 ± 16 to 70 ± 28 ml) increased with exercise as did stroke volume (68 ± 19 to 95 ± 22 ml) and cardiac output (5.1 ± 0.8 to 11.6 ± 2.8 liters/min). One patient had a wall motion abnormality during rest that persisted during exercise, and six patients exhibited new wall motion abnormalities during exercise.

Comparison of the radionuclide angiocardiographic data in the patients with mitral valve prolapse and normal coronary anatomy (Group II) with those of the patients with mitral valve prolapse and significant coronary artery disease (Group III) documented important hemodynamic differences (Table II). The two groups were not different at rest, and the differences between these two groups developed only during exercise. During exercise to a lower heart rate, the group with mitral valve prolapse and coronary disease (Group III) had a lower ejection fraction and a larger end-systolic volume than did Group II.

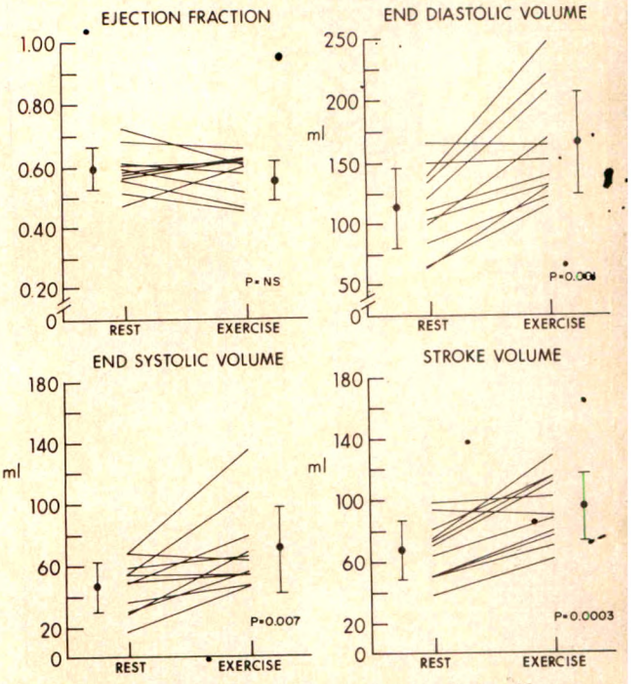

FIGURE 3. Group III. Effects of exercise in 11 patients with coronary artery disease and mitral valve prolapse. The ejection fraction decreased in six patients in whom wall motion abnormalities developed with exercise.

Comparison of patients with mitral valve prolapse diagnosed with angiocardiography and echocardiography: The changes in ventricular function with exercise in patients with echocardiographic documentation of mitral valve prolapse (Group IV) were similar to those in patients with prolapse and normal coronary anatomy (Group II) (Fig. 4). Seven of the 11 patients achieved 85 percent of the age-predicted target heart rate, and the mean heart rate increased from 9[illegible] ± 24 beats/min at rest to 152 ± 16 beats/min during exercise. The change in blood pressure from rest to exercise was 91 ± 9 to 101 ± 13 mm Hg. The average ejection fraction increased during exercise (0.67 ± 0.0[illegible] to 0.73 ± 0.07), and only one patient had a decrease in ejection fraction during exercise. The end-diastolic volume increased during exercise (106 ± 36 to 117 ± 4[illegible] ml); end-systolic volume was not changed from rest t[illegible]

TABLE II

Comparison of Groups II and III* by Analysis of Variance

	HR	BP	EF	EDV	ESV	SV	CO
Rest	NS	NS	NS	NS	NS	NS	NS
Ex	(II > III); p = 0.001	NS	(II > III); p = 0.0004	NS	(II < III); p = 0.0001	NS	NS

* Group II, patients with mitral valve prolapse and normal coronary angiograms; Group III, patients with mitral valve prolapse and coronary arterial stenosis on angiography. Abbreviations as in Table I.

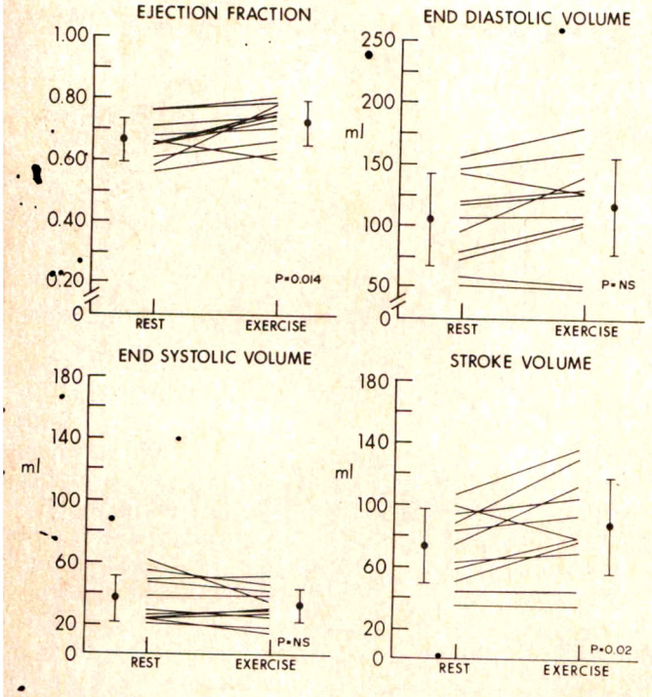

FIGURE 4. Group IV. Response to exercise in 11 patients with mitral valve prolapse diagnosed by echocardiography. The ejection fraction and stroke volume increased with exercise.

exercise (35 ± 15 to 31 ± 11 ml). Stroke volume (71 ± 24 to 86 ± 32 ml) and cardiac output (6.3 ± 2.0 to 13.0 ± 5.2 liters/min) increased during exercise. No patient in Group IV demonstrated wall motion abnormalities during rest or exercise.

Differences in radionuclide angiocardiographic results between the patients with mitral valve prolapse on echocardiography (Group IV) and those with mitral valve prolapse and normal coronary anatomy (Group II) were apparent only during rest (Table III). During rest, the patients with mitral valve prolapse on echocardiography had a lower mean blood pressure that probably reflects the younger age of this group. During exercise, there were no differences between these two groups in any hemodynamic measurement.

Discussion

Since the clinical description of the mitral valve prolapse syndrome by Barlow et al.,[12,13] the cause of the prolapse and its relation to ventricular function have repeatedly been examined.[1,2,14] Left ventricular hemodynamic measurements in patients at rest are frequently normal or reflect the pathophysiology of mitral regurgitation.[1,15,16] Stress-induced myocardial perfusion abnormalities have been documented in patients with mitral valve prolapse, but most of these patients also had coronary artery disease.[17–19] However, changes in ventricular function from rest to exercise in patients with mitral valve prolapse alone and in patients with concomitant coronary artery disease have not been examined.

Exercise-induced changes in left ventricular function demonstrated by radionuclide angiocardiography are sensitive and specific indicators of myocardial ischemia secondary to coronary artery disease.[20] Regions of myocardium that become ischemic during exercise result in wall motion abnormalities and a decrease in global ejection fraction.[5,6,21,22] False negative radionuclide angiocardiographic results occur most frequently in patients with single vessel coronary disease and in patients who fail to achieve an adequate exercise level.

Recognition of mitral valve prolapse by angiocardiography versus echocardiography: The purpose of this investigation was to assess (1) whether hemodynamic alterations could be measured during exercise in patients with mitral valve prolapse alone, and (2) whether these patients could be differentiated from a similar group of patients with mitral valve prolapse and concomitant coronary artery disease. Isolation of these homogeneous patient populations required retrospective review of studies in a large number of patients. Whereas it would have been ideal to have patient populations with mitral valve prolapse documented with both cardiac catheterization and echocardiography, very few patients met these criteria. The patients with mitral valve prolapse diagnosed with echocardiography (Group IV) differed from those whose diagnosis was made by cardiac catheterization in that the age and presenting symptoms of the former patients were not strongly suggestive of coronary artery disease. Therefore, confirmation of the clinical diagnosis of mitral valve prolapse by echocardiography commonly completed the diagnostic evaluation and cardiac catheterization was not recommended. In contrast, the diagnostic consideration of coronary artery disease was the primary motivation for cardiac catheterization in patients in Groups I, II and III, and cardiac catheterization was commonly the final step in evaluation of these patients.

Although it is not possible to state definitely that patients in Group IV had no coronary artery disease, the similar response to exercise in Groups II and IV suggests

TABLE. III

Comparison of Groups II and IV* by Analysis of Variance

	HR	BP	EF	EDV	ESV	SV	CO
Rest	NS	(II > IV); p = 0.04	NS	NS	NS	NS	NS
Ex	NS	NS	NS	NS	NS	NS	NS

* Group II, patients with mitral valve prolapse and normal coronary angiograms. Group IV, patients with mitral valve prolapse on echocardiography but no other demonstrable cardiac disease. Abbreviations as in Table I.

the absence of significant disease. If differences had occurred between these two groups, it would not be possible to conclude whether the cause was the presence of coexistent coronary artery disease in Group IV or the differences in patients diagnosed to have prolapse by angiographic or echocardiographic criteria. The absence of significant hemodynamic changes in the two groups during rest and exercise is strong evidence that recognition of mitral valve prolapse by either diagnostic modality is not associated with hemodynamic alteration that can be recognized by radionuclide measurements of left ventricular function at rest or exercise.

Radionuclide angiocardiography in differentiating mitral valve prolapse with or without coronary artery disease: Stress myocardial scintigraphy using thallium-201 has been observed to differentiate patients with mitral valve prolapse syndrome from those with coronary artery disease and mitral valve prolapse.[17,19] This study suggests that the two disease entities can also be differentiated by changes in ventricular function from rest to exercise determined with radionuclide angiocardiography. Each of the 11 patients with normal coronary anatomy and mitral valve prolapse demonstrated changes in ventricular function similar to those in patients with normal coronary anatomy and no mitral valve prolapse. During exercise, the ejection fraction increased, and no wall motion abnormalities developed in both groups. Therefore, the presence of mitral valve prolapse alone caused no measurable detrimental effect on ventricular function during rest or exercise.[23] In contrast, changes in ventricular function with exercise in patients with concomitant mitral valve prolapse and coronary disease appear to reflect the presence and severity of the coronary artery disease rather than prolapse. Although only 1 of the 11 patients with both diseases achieved an adequate exercise level, 6 had a decreased ejection fraction and exhibited wall motion abnormalities with exercise.

Implications: Changes in ventricular function from rest to exercise assessed with radionuclide angiocardiography can distinguish patients with mitral valve prolapse alone from those with prolapse and coronary artery disease. Patients with mitral valve prolapse alone had uniform increases in ejection fraction and no wall motion abnormalities with exercise, whereas patients with both prolapse and coronary disease frequently demonstrated decreased ejection fraction and wall motion abnormalities provoked during a lower exercise level. Therefore, exercise-induced decreases in ejection fraction and wall motion abnormalities in patients with prolapse diagnosed with echocardiography would suggest the presence of concomitant significant coronary disease.

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Exercise Cross-Sectional Echocardiographic Diagnosis of Coronary Artery Disease

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To test the feasibility of detecting transient left ventricular regional wall motion abnormalities during exercise-induced myocardial ischemia, 55 patients undergoing diagnostic coronary arteriography were studied in a prospective blinded manner with wide angle cross-sectional echocardiography. The ultrasonic studies were obtained with the patients at rest and during exercise in the supine position using a bicycle ergometer. Cross-sectional echocardiographic studies during exercise were adequate for analysis in 43 (78 percent) of the 55 patients. Forty-one of the 43 manifested either a new regional wall motion abnormality during exercise (20 subjects) or wall motion that remained entirely normal during exercise (21 subjects); in two subjects an abnormal wall motion abnormality at rest did not change with exercise. Nineteen of the 20 patients with a new regional wall motion abnormality had significant coronary artery disease and 15 of these 19 had S-T segment depression during bicycle ergometry. The one patient with a normal coronary arteriogram had an early cardiomyopathy. Ten of the 21 subjects with normal wall motion at rest and during exercise had a normal coronary arteriogram, whereas 11 had evidence of important anatomic coronary artery disease and thus had a false negative echocardiographic findings. Six of these 11 patients had S-T segment depression during exercise. The usefulness of exercise echocardiography to predict coronary artery disease was not altered even when only 26 patients without previous myocardial infarction and with a normal cross-sectional echocardiogram at rest were considered. Thus, new regional wall motion abnormalities during exercise as identified with cross-sectional echocardiography represent a specific finding for the presence of coronary artery disease. However, normal regional wall motion during exercise does not exclude the presence of important anatomic coronary artery disease.

Echocardiography has been used as a reliable method of detecting myocardial ischemia or infarction, or both, by demonstrating regional left ventricular wall motion abnormality at rest.[1–3] However, without prior myocardial infarction or acute ischemia, patients with severely obstructed coronary arteries frequently have normal left ventricular wall motion at rest.[4,5] During exercise, increased oxygen demand may outstrip the limited supply from a diseased coronary artery, thus precipitating acute myocardial ischemia with associated abnormal regional wall motion.[6–9] New regional wall motion abnormalities as a sign of coronary artery disease were demonstrated during exercise-induced ischemia with left ventricular cineangiography[10,11] and cardiac nuclear imaging techniques.[12,13] Studies[14–16] during acute coronary arterial ligation in the dog showed that, with the onset of ischemia, rapid deterioration of regional wall motion occurred even before the development of S-T segment changes in the electrocardiogram. These myocardial alterations were immediately reversible on release of the coronary ligature.

The potential for using exercise as a means of inducing regional wall motion abnormalities while imaging the heart with echocardiography

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was reported by Mason et al.,[8] using the M mode technique. Unfortunately, this technique is limited in the extent of myocardium that can be imaged; and only 45 percent of their studies were considered adequate for analysis. The use of cross-sectional echocardiography to detect regional wall motion abnormality provides a better visual orientation and was recently explored by Wann et al.[9] However, their study was limited to a 30° mechanical sector scan of the myocardium in which endocardial images were not well demonstrated. In this study we attempted to test the feasibility of detecting transient left ventricular regional wall motion abnormalities during exercise-induced myocardial ischemia using wide angle cross-sectional echocardiography to predict the presence of coronary artery disease.

Methods

Patients: Fifty-five patients, 40 men and 15 women with a mean age (± standard deviation) of 52 ± 11 years undergoing diagnostic coronary arteriography were studied in a prospective blinded manner. All patients had a clinical chest pain syndrome considered consistent with angina pectoris. Patients who had a recent myocardial infarction, valvular heart disease, unstable angina pectoris, congestive heart failure or overt arrhythmia were excluded primarily because exercise testing would have been inadvisable under these conditions. Evidence of prior myocardial infarction (3 or more months) by 12 lead scalar electrocardiography was present in 18 of the 55 patients.

Echocardiographic technique: Cross-sectional and M mode echocardiograms were obtained within 24 hours before cardiac catheterization with use of a wide angle, three element rotary mechanical sector scanner (ATL Mark III). A standard cross-sectional echocardiographic study was obtained at rest in which the left ventricular long axis, multiple short axis and apical views of the left ventricle were imaged. Patients exercised in the supine position using a bicycle ergometer (Quinton Imaging Ergometer Table 845T) with the patient's upper torso and head held fixed by restraints. Exercise was performed at an initial work load of 200 kg.m/min. for 3 minutes with an increase of 100 kg.m every 3 minutes. The test was stopped because of the development of chest pain, 2 mm or greater S-T segment depression or exhaustion. A full 12 lead electrocardiogram (Marquette Electronics, Inc., Milwaukee, Wisconsin) and sphygmomanometer-determined blood pressure were recorded each minute throughout the test. During exercise the echocardiographic transducer was constantly held on the patient's precordium in order to visualize primarily the short axis view of the left ventricle from the level of the mitral valve through that of the cardiac apex. During peak exercise the transducer was rotated to visualize the long axis and apical four chamber left ventricular views.

Cross-sectional echocardiograms were recorded on a Sanyo (model 7100) 0.5 inch (1.27 cm) videotape recorder and were later analyzed by three independent observers without knowledge of the clinical findings or cardiac catheterization data. There was concordant interobserver analysis in 95 percent of cases. Intraobserver variability was not tested. Figure 1 depicts the left ventricular walls seen in each echocardiographic view in which motion was qualitatively analyzed. Abnormal wall motion was identified by comparing the wall motion of that particular segment with that of all other segments of the heart and was graded as hypokinetic, akinetic or normal.

Cardiac catheterization: Left ventriculography was performed using either the Sones or Judkins technique in the right anterior oblique position. Coronary angiograms were analyzed by two independent observers for the degree of stenosis of the right, left main, left anterior descending and left circumflex (or its marginal branch) coronary artery. A vessel was considered to have important obstruction if 50 percent or more of its lumen was narrowed in diameter.

Results

Our technique of exercise cross-sectional echocardiography required approximately 1 hour to complete from preparation through the patient recovery period. Cross-sectional echocardiographic studies during exercise were adequate for analysis in 43 (78 percent) of the 55 patients. The mean age of these 43 patients was 51 ± 11 years and 29 were men. Eleven of the 12 inadequate studies were in men whose mean age was 57 ± 6 years (Table I). The major technical limitation during

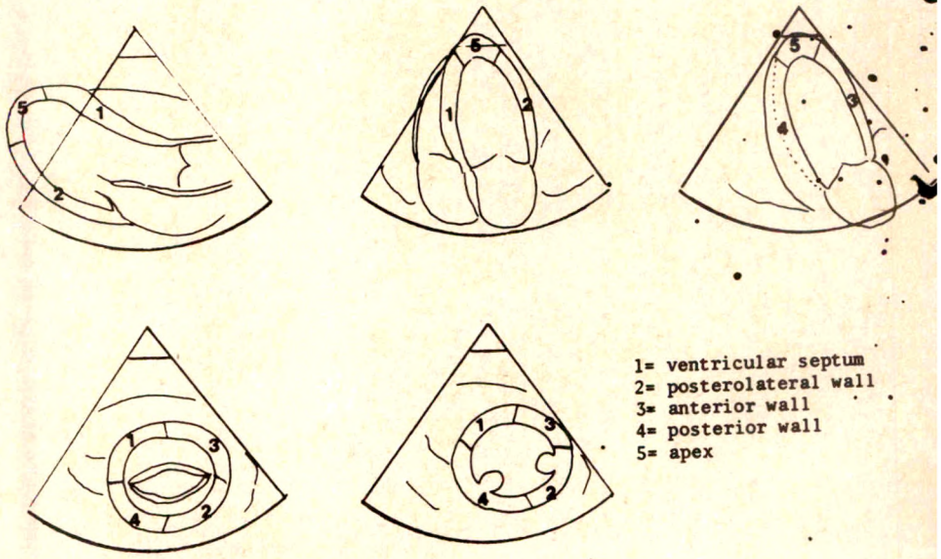

FIGURE 1. Schematic drawings representing **(from upper left to lower right)** the left ventricular long axis, apical four chamber, apical two chamber and short axis views, first at the mitral valve and then at the papillary muscle level, demonstrating the location of the left ventricular wall segments used during data analysis.

exercise was hyperventilation because the motion of the upper thorax was held stationary by the use of restraints. Exercise studies primarily focused on data from the sternal approach to the short axis of the left ventricular scanning from the level of the mitral valve to that of the cardiac apex because these views provided the best endocardial definition. Patients receiving propranolol therapy are listed in Table I.

Wall motion at rest and during exercise: Comparison of the resting cross-sectional echocardiogram with the single plane right anterior oblique left ventricular angiogram revealed that both studies showed normal regional wall motion in 23 patients and abnormal regional wall motion in 9 patients. A normal resting echocardiogram but mildly abnormal ventriculogram (showing hypokinesia) was seen in nine subjects (anterior wall in five, posterior in three and diffuse in one). In two subjects the ventriculogram was normal at rest but posterior hypokinesia was evident in the echocardiogram at rest.

Forty-one of the 43 subjects with adequate studies had either a new or increased regional wall motion abnormality during exercise (n = 20) or the wall motion remained entirely normal during exercise (n = 21). Two subjects (Patients 22 and 24) had abnormal resting left ventricular wall motion that did not change during exercise echocardiography; both patients had significant coronary artery disease.

TABLE 1

Characteristics of 43 Study Patients

Case	Age (yr) & Sex	Prior MI	Pro-pran-olol Therapy	Supine Ergometry		Two Dimensional Echocardiography			M Mode Echo-cardiography	Vessels With CAD (n)
				S-T↓	Pain	Rest	Excercise	Recov-ery		
1	54M	−	−	2	−	NI	↓VS,↓A	NI	NI	3
2	59M	+	+	0	+	↓VS,↓P	↓↓VS,↓P	↓VS,↓P	↓VS	3
3	67M	+	+	4	+	NI	↓VS, ↓↓P	NI	NI	3
4	69F	+	+	0	−	NI	NI	NI	NI	2
5	44M	−	+	0	−	NI	↓A, ↓PL, P	NI	NI	0*
6	58M	−	−	0	−	NI	NI	NI	NI	3
7	58M	−	−	0	−	NI	NI	NI	NI	0
8	36F	−	−	0	−	NI	NI	NI	NI	0
9	44M	−	−	1	−	NI	NI	NI	NI	2
10	47F	−	+	3	−	NI	NI	NI	NI	3
11	33F	−	−	2	−	↓VS, ↓A	↓↓VS,A,↓P	↓VS,↓A	↓VS	2
12	50F	−	−	0	−	NI	NI	NI	NI	0
13	67M	−	−	0	−	↓↓VS,↓P,A	↓↓VS,↓↓A,↓↓P	↓↓VS,↓P,A	↓VS	3
14	62F	+	−	1	−	NI	NI	NI	NI	3
15	37F	+	−	0	−	NI	NI	NI	NI	3
16	55M	+	−	1	−	NI	↓VS,↓PL,P	↓VS,PL, P	↓P	3
17	34M	−	−	0	−	NI	NI	NI	NI	0
18	52M	+	+	2.5	−	↓A, ↓P	↓VS,↓A,↓P	↓A, ↓P	NI	3
19	60F	−	−	2	−	NI	↓VS,↓A	NI	↓VS	1
20	36M	−	−	0	−	NI	NI	NI	NI	0
21	49M	+	+	3	−	↓↓P	↓A,↓↓P	↓↓P	NI	3
22	52M	−	−	0	−	↓P,A, VS	↓↓P,↓A,VS	↓P,A,VS	↓VS	3
23	46F	−	−	0	−	NI	NI	NI	NI	2
24	36M	+	+	0	−	↓A,↓PL	↓A,↓PL	↓A,↓PL	NI	1
25	59M	−	−	0	−	NI	NI	NI	NI	0
26	48M	−	−	1	−	NI	NI	NI	NI	2
27	63M	+	−	2	−	↓P	↓↓P,↓PL	↓P	NI	3
28	48F	−	−	0	−	NI	NI	NI	NI	0
29	61F	−	+	0.5	−	NI	NI	NI	NI	1
30	30M	−	−	1	−	↓↓VS	↓↓VS,↓P	↓VS	NI	2
31	45M	−	+	3	−	NI	↓↓PL, ↓VS	NI	NI	2
32	26F	−	−	0	−	NI	NI	NI	NI	0
33	53M	−	−	1.5	−	NI	NI	NI	NI	1
34	65F	−	−	1.0	−	NI	NI	NI	NI	0
35	52M	+	−	0	−	NI	↓P, ↓PL	NI	NI	2
36	42M	−	−	2	−	NI	↓VS	NI	NI	1
37	60F	+	+	1	−	↓P	↓VS,P,PL	↓P	NI	1
38	70M	−	−	1.5	−	NI	↓PL,P	NI	NI	3
39	39M	−	+	0.5	+	NI	↓P	NI	NI	3
40	58M	+	−	0	−	NI	NI	NI	NI	3
41	55M	−	+	0	−	↓A	↓VS,↓A	↓A	NI	1
42	44M	−	−	0	−	NI	NI	NI	NI	0
43	62M	−	+	3	+	NI	↓VS,↓A	NI	NI	3

* Occult idiopathic congestive cardiomyopathy on left ventricular angiography.

A = anterior wall; CAD = coronary artery disease; MI = myocardial infarction; NI = normal wall motion; P = posterior wall; PL = posterolateral wall; S-T↓ = mm of S-T segment depression during supine ergometry; VS = ventricular septum ↓ = hypokinetic; ↓↓ = akinetic; + = present; − = absent.

Correlation with coronary arteriographic findings: Twenty of 41 patients had a new regional wall motion abnormality on cross-sectional echocardiography during exercise and 19 of the 20 had significant coronary artery disease (three vessel disease in 11, two vessel disease in 4, and one vessel disease in 4). Fifteen of these 19 patients had S-T segment depression during bicycle ergometry, whereas 4 did not. The one patient with a normal coronary arteriogram had evidence of an early cardiomyopathy on left ventricular cineangiography with diffuse hypokinesia and an elevated left ventricular end-diastolic pressure.

Twenty-one of the 41 patients had normal left ventricular wall motion on echocardiography at rest and during exercise. Ten (48 percent) of these 21 patients had a normal coronary arteriogram; 9 had no S-T segment abnormalities on exercise, and the other patient had 2 mm S-T segment depression. Eleven (52 percent) of the 21 patients had important anatomic coronary artery disease and thus had a false negative echocardiographic response. Six of the 11 had S-T segment depression during exercise, whereas 5 did not. Four of the 11 patients had three vessel, 5 had two vessel and 2 had one vessel coronary artery disease. Figures 2 and 3 show a normal echocardiographic study at rest and during exercise, respectively, a patient with normal coronary angiographic findings and a patient with three vessel coronary artery disease (false negative response). Figure 4 demonstrates the echocardiogram of a patient who manifested a new regional wall motion abnormality on exercise and who had coronary artery disease (true positive response).

Correlation in patient group without previous myocardial infarction: The overall results were not altered when only the 26 patients with adequate cross-sectional echocardiograms, no prior myocardial infarction and a normal cross-sectional echocardiogram at rest were studied. Nine of the 26 had a new regional wall motion abnormality on exercise, and 8 of these 9 had significant coronary artery disease (4 had three vessel, 2 had two vessel and 2 had one vessel disease). Of these eight patients, six had S-T segment depression induced with bicycle ergometry and two did not. Once again one patient had normal coronary angiographic findings and his new regional wall motion abnormality was judged to be caused by an early cardiomyopathic

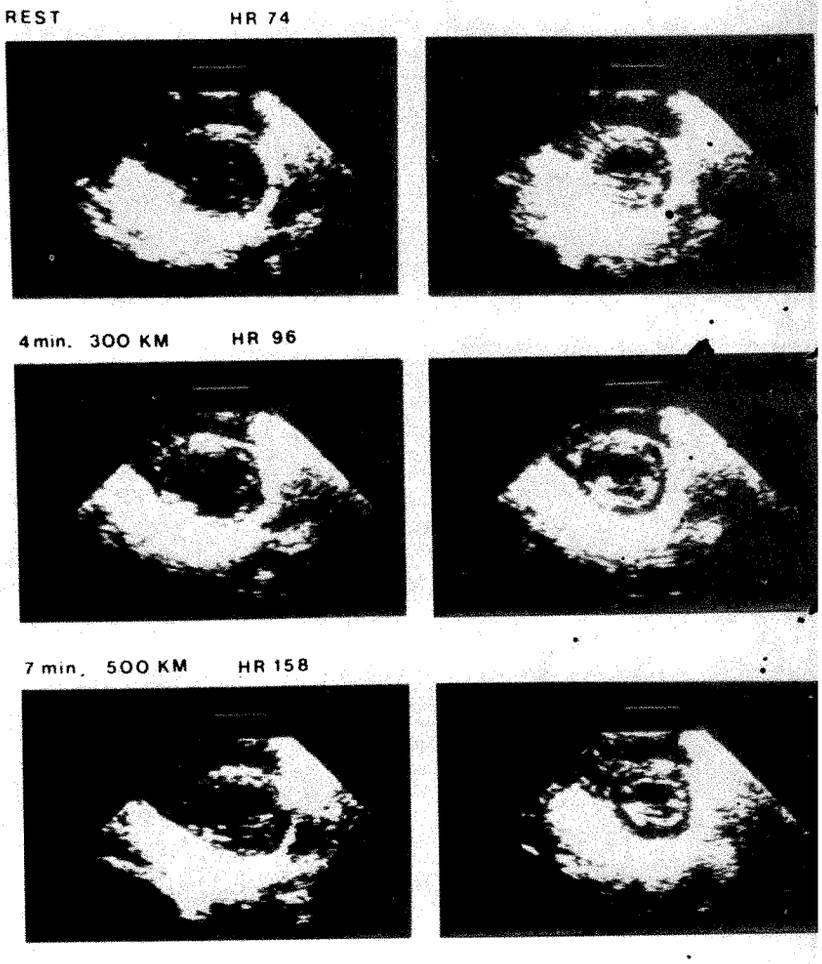

FIGURE 2. Left ventricular short axis views during end-diastole (**left panels**) and end-systole (**right panels**) in a patient with normal coronary arteriographic findings. The echocardiographic studies were taken at rest (heart rate [HR] 74 beats/min) and during supine ergometry first at 4 minutes at a work load of 300 kg.m and then at 7 minutes at a work load of 500 kg.m. Note that there is normal contraction during systole of all left ventricular wall segments and that qualitatively the end-systolic volume was decreased at peak exercise compared with the resting state, suggesting an increase in regional ejection fraction.

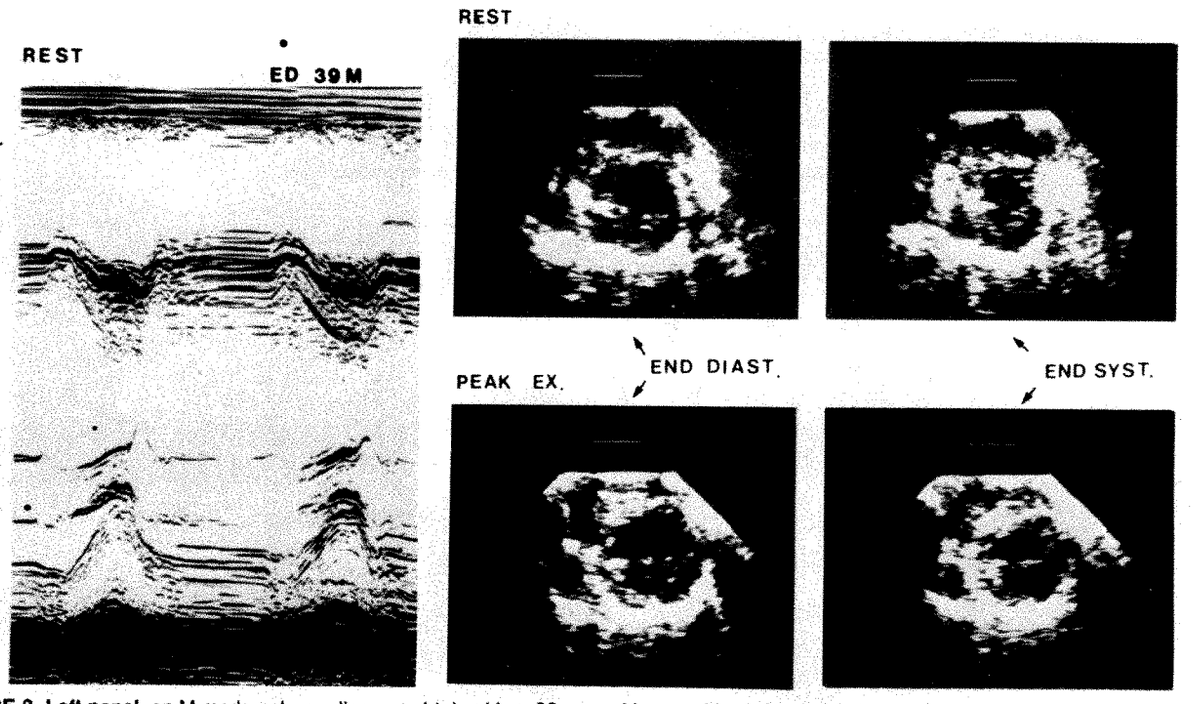

FIGURE 3. Left panel, an M mode echocardiogram obtained in a 39 year old man with angina pectoris and three vessel coronary artery disease demonstrating at rest normal ventricular septal and posterior left ventricular wall motion. **Right panel,** left ventricular short axis views at the level of the papillary muscles demonstrating end-diastole (DIAST.) on the left and end-systole (SYST.) on the right. Left ventricular wall motion remained normal at rest and during exercise (EX).

state. Seventeen of the 26 patients had normal cross-sectional echocardiogram at rest and during exercise. Ten (59 percent) of the 17 had a normal coronary arteriogram, including 9 who had no abnormality in the S-T segment response to ergometry. The other seven (41 percent) had coronary artery disease (three vessel in one, two vessel in four and one vessel in two) and four of the seven had S-T segment depression on bicycle ergometry. These patients therefore had a false negative response. Thus, with exclusion of regional wall motion abnormalities at rest or prior myocardial infarction, the percent of false negative responses changed from 52 to 41 percent.

Discussion

In the classic study by Tennant and Wiggers,[17] acute coronary arterial ligation in the dog produced immediate abnormal contraction of the left ventricular myocardial segment supplied by that coronary artery. This has been shown with a wide variety of techniques[1–9] to occur in human beings during acute ischemia and acute myocardial infarction. The mechanical abnormalities with ischemia occur within seconds and disappear rapidly with reversal of ischemia.[14–16] Both exercise cineangiography and cardiac nuclear imaging techniques have demonstrated new areas of left ventricular wall motion abnormality during acute ischemia that disappear rapidly after ischemia is reversed. M mode echocardiography has been limited because of its relatively narrow view of the myocardium and small proportion of adequate studies. Two dimensional echocardiography provides the ability to view the major area of the myocardium during exercise and approximately 75 percent of these studies are adequate for analysis. This is a higher proportion than that reported for M mode echocardiography probably because of the better spatial orientation and more easily identified landmarks during two dimensional echocardiography. The increased field of view of the wide angle two dimensional echocardiographic equipment as used in this study allows for a more precise identification of regional wall motion abnormalities than is possible with M mode echocardiography or narrow two dimensional echocardiographic sector scanners.

Sensitivity of two dimensional echocardiography on exercise: The results of our study, similar to those of Wann et al.,[9] demonstrate that patients who manifest new regional wall motion abnormalities during exercise invariably have coronary artery disease. However, one patient (5 percent) did have left ventricular regional wall motion abnormalities probably because of an occult cardiomyopathy rather than coronary artery disease. Although abnormal regional wall motion on two dimensional echocardiography during exercise appeared to be highly specific for the presence of coronary artery disease, its absence did not predict a high likelihood of a normal coronary arteriogram. About 50 percent of our patients with normal regional wall motion during exercise had important anatomic coronary artery disease. Thallium-201 myocardial perfusion scanning was not

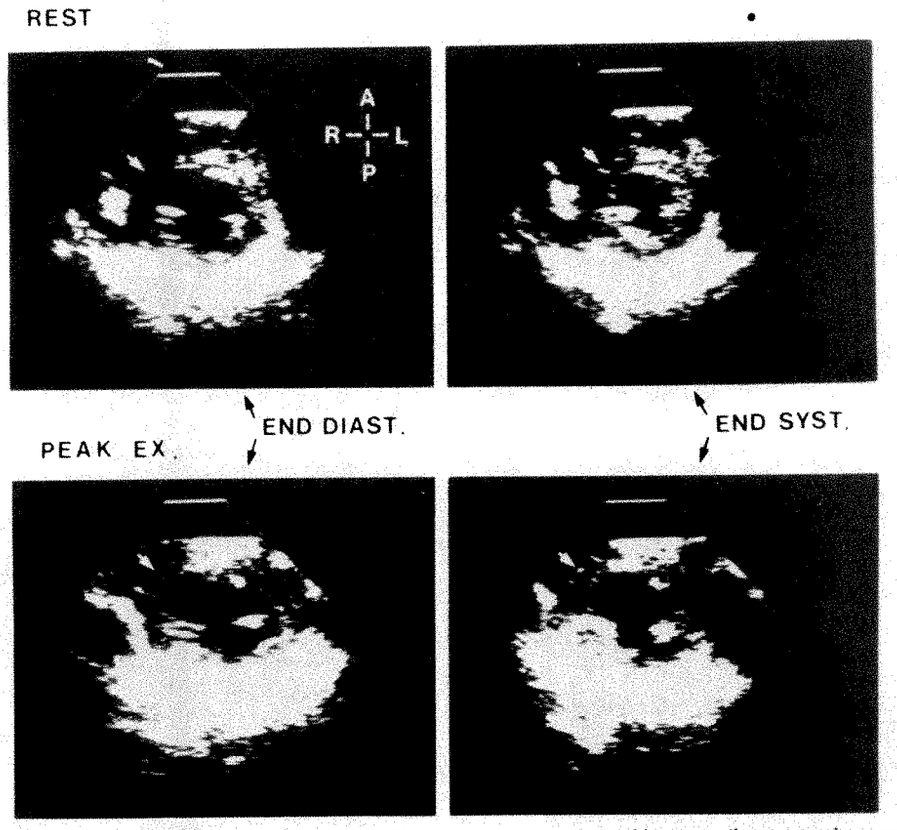

FIGURE 4. Left ventricular short axis views at the level of the papillary muscle in a patient with severe three vessel coronary artery disease and angina pectoris depicting end-diastole (DIAST.) at left and end-systole (SYST.) at right. The **small white arrow** points to the ventricular septum, which has normal motion during systole in the resting state, but becomes akinetic during peak exercise (EX.). The apparent increase in end-systolic volume during peak exercise suggests a decrease in regional ejection fraction.

available in these patients to permit determination of whether the coronary obstructive disease, although anatomically important, was associated with a myocardial perfusion deficit. However, approximately 50 percent of these patients had abnormal S-T segment depression during exercise testing. Thus, it appeared that the electrocardiographic manifestation of ischemia in these patients was more sensitive in predicting the presence of anatomic coronary artery disease than was the presence of new regional wall motion abnormalities on two dimensional echocardiography during exercise. This is in distinct contrast to a much higher sensitivity for the prediction of coronary artery disease by detecting abnormal regional wall motion during exercise radionuclide studies.[12]

Our results were not altered when those patients with resting regional wall motion abnormality on echocardiography were excluded or when the use of propranolol was considered. Of the 14 patients receiving propranolol, 10 had a new regional wall motion abnormality on exercise; 9 of these had coronary artery disease and the other an occult cardiomyopathy. The other four patients had no new regional wall motion abnormality during exercise echocardiography, even though they all had coronary artery disease.

The exercise protocol used in this echocardiographic study relied on the supine rather than the upright position which is commonly used for the standard treadmill exercise test. The supine position was considered adequate to induce ischemia because it is associated with a sufficient increase in blood pressure and heart rate to induce ischemia.[18] Similar protocols are used in radionuclide angiography and, thus, the variance in sensitivity between two dimensional echocardiography and radionuclide angiography cannot be explained by the degree or type of exercise employed. Relative limitations of two dimensional echocardiography in viewing the entire ventricle at once (which can be done by radionuclide angiography) is a potential factor.

Clinical implications: Because two dimensional exercise echocardiography is noninvasive, easily repeatable and inexpensive, determines instantaneous events and does not impose a potential radiation hazard, it may prove to have a useful role in the noninvasive detection of coronary artery disease. It appears to identify new regional wall motion abnormalities during exercise that, when present, specifically indicate the presence of coronary artery disease. However, it may show normal findings in about 50 percent of patients with such disease.

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Importance of Coronary Collateral Circulation in Interpreting Exercise Test Results

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The importance of the coronary collateral circulation as a cause of false negative exercise tests was studied in 37 patients who had a 90 percent or greater isolated stenosis of the luminal diameter in one major coronary artery. Sixteen patients had large collateral vessels and 21 patients had either minimal or no collateral circulation. Myocardial scintigraphy was performed in 22 of the 37 patients.

The final treadmill time was similar in both groups (521 ± 192 versus 554 ± 144 seconds [mean ± standard error of the mean]). The presence and depth of S-T segment depression was not influenced by the degree of collateralization. The sensitivity of the exercise electrocardiogram was greater for patients with disease in the left anterior descending than in the right or left circumflex coronary arteries (95 versus 60 percent, $p < 0.03$). Among the 22 patients with thallium-201 scintigrams, myocardial perfusion defects were more common in patients without collateral circulation (100 versus 40 percent, $p < 0.01$) and involved more myocardial segments ($p < 0.005$). The overall sensitivity of exercise electrocardiography for the detection of single vessel stenosis 90 percent or greater was similar to that of myocardial scintigraphy (81 versus 73 percent).

In conclusion, large intercoronary collateral vessels are not a cause of false negative exercise electrocardiograms in patients with single vessel disease but are a common cause of false negative scintigrams. Large collateral vessels may limit the quantity and location of myocardial ischemia, but exercise electrocardiography and thallium-201 scintigraphy may detect different aspects of ischemia.

Single vessel coronary artery disease is a common cause of false negative results in diagnostic stress testing.[1–6] The addition of thallium-201 scintigraphy to such testing has increased the detection of patients with single vessel disease but false negative results are still common in patients with isolated right or left circumflex coronary artery disease.[7–14] There are few data that evaluate the role of the coronary collateral circulation as a possible cause of false negative tests. Clearly, if large well developed collateral vessels distal to a high grade coronary arterial stenosis could prevent or rapidly reverse transient myocardial ischemia, no significant electrocardiographic changes or perfusion defects would be observed. This study examines the hypothesis that coronary collateral circulation can cause false negative exercise electrocardiograms and myocardial scintigrams.

Methods

Study patients: The study group consisted of 37 patients with single coronary arterial stenosis equal to or greater than 90 percent of the luminal diameter in one of the three major coronary arteries and no other arterial stenosis of 50 percent or greater. All patients had chest pain for at least 6 months before cardiac catheterization. There were 26 men and 11 women whose mean age was 47 years (range 26 to 62). Patients with a previous myocardial infarction, cardiomyopathy or valvular heart disease were excluded.

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Electrocardiographic exercise test: Each patient underwent a maximal symptom-limited stress test performed with use of 14 electrocardiographic leads according to a modified Bruce protocol.[15,16] A test was considered positive if horizontal or downsloping S-T segment depression of 1 mm or more or a slow upsloping S-T segment depressed 2 mm or more at 0.08 second after the J point occurred.[15–17] All patients with a negative test achieved at least 85 percent of their age-predicted maximal heart rate.

Myocardial scintigraphy: Myocardial scintigraphy was performed in 22 of the 37 patients after 2 millicuries (mCi) of thallium-201 was injected intravenously 45 to 60 seconds before terminating exercise. Anteroposterior, 30° left anterior oblique and left lateral views were obtained using standard techniques. The total of 150,000 counts/view over the left ventricle were registered with a Picker-Dyna 4/5 gamma camera equipped with a high resolution collimator and a 20 percent window. Counts originating from the spleen or liver were avoided using a 12 cm leaded mask. The scintigrams were photographed in black and white on 70 mm film after 30 percent background subtraction and a 9 point matrix smoothing. The scintigram at rest was obtained 4 to 10 days after exercise.

The scintigrams were interpreted qualitatively by three observers unaware of the clinical status, exercise test results or location of the diseased vessel. The test was considered positive if a localized reversible perfusion defect was present. The extent of the defect was analyzed semiquantitatively by dividing each scintigram into five segments as described by Rigo et al.[18] The myocardial segments corresponding to each coronary artery were considered in order to quantify the extent of myocardial ischemia.

Assessment of collateral circulation: Coronary angiography was performed using the transfemoral approach.[19] A coronary arterial stenosis of 90 percent or greater of the luminal diameter was considered a significant lesion for the purpose of this study; this degree of narrowing is usually required to demonstrate collateral vessels at angiography. The presence of collateral circulation was assessed by an experienced cardiovascular radiologist unaware of the results of noninvasive testing.[20] The average ejection fraction calculated by the area-length method[21] was 0.62 ± 0.08 (mean ± standard error of the mean).

Statistical analysis: The differences between groups were analyzed using the chi-square test for nonparametric variables and the unpaired *t* test and analysis of variance for parametric variables.

Results

Coronary angiography: Obstructive coronary artery disease (90 percent or greater stenosis of the luminal diameter) was present in the left anterior descending coronary artery in 22 patients, in the left circumflex coronary artery in 5 patients and in the dominant right coronary artery in 10 patients. The patients were classified into two groups on the basis of the degree of collateralization. In group A (n = 16 patients), the distal segment of the stenosed vessel was clearly opacified and large intercoronary collateral vessels were visible. Group B (n = 21 patients) was characterized by minimal or absent collateral blood flow (involving only the interseptal-intermarginal branches).

Exercise electrocardiography: The physiologic limitation to exercise was greatest in patients with left anterior descending arterial stenosis. These patients had a final treadmill exercise time of 481 ± 177 (mean ± standard deviation) seconds versus 626 ± 98 seconds in patients with either right or left circumflex coronary artery disease ($p < 0.05$). Exercise was terminated by angina in 91 percent of patients (20 of 22) with but in only 20 percent of patients (3 of 15) without left anterior descending arterial stenosis ($p < 0.005$). The patients with left anterior descending stenosis of the left anterior descending common artery had more ischemic electrocardiographic responses than did those with right or left circumflex coronary arterial stenosis (95 percent [21 of 22] versus 60 percent [9 of 15]; $p < 0.03$). However, among the 30 patients with a positive electrocardiographic test the number and location of positive leads, depth of S-T segment depression and duration of ischemia after exercise did not correlate with the location of the diseased vessel. Leads V_4 to V_6, CC_5 or CM_5 recorded significant S-T segment depression in the patients with right or left circumflex coronary artery disease.

The presence and depth of S-T segment depression was not influenced by the degree of coronary collateralization (Fig. 1). Of 16 patients in group A (with collateral vessels), 94 percent had a positive electrocardiographic test compared with 71 percent of the 21 patients in group B (without collateral vessels) (difference not significant [NS]). The maximal treadmill time was 521 ± 192 seconds for patients in group A compared with 554 ± 144 seconds in patients in Group B. The maximal pressure-rate product was also similar in both groups. The frequency of angina during exercise was 56 percent (9 of 16) patients in Group A and 67 percent (14 of 21) in patients in group B (difference not significant).

Myocardial scintigraphy: Exercise thallium-201

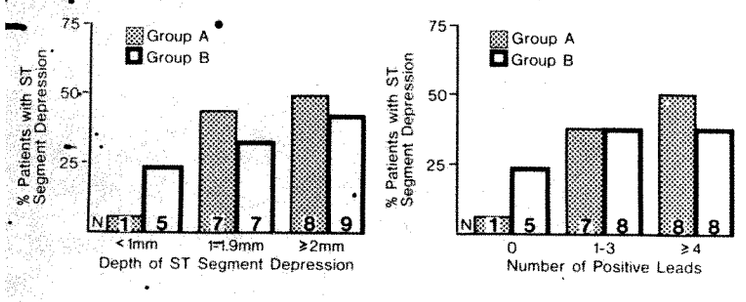

FIGURE 1. The depth of S-T segment depression (**left**) and the number of positive electrocardiographic leads (**right**) was similar in patients with (group A) and without (group B) collateral vessels.

TABLE I

Correlation of Exercise Electrocardiographic and Scintigraphic Results With Coronary Angiography

Case	Age (yr) & Sex	Exercise Test: Leads Positive	Exercise Test: Max S-T Depression	Exercise Test: Angina	Exercise Test: Max HR (per min)	Exercise Test: Final TT (s)	Thallium Perfusion Defect: Rest/Ex	Thallium Perfusion Defect: Location	Angiography: % Stenosis	Angiography: Collateral Vessels
Group A: Patients With Collateral Vessels										
1	46M	CM_5	1.5	+	156	210	+/++	Septal	100% LAD	RCA → LAD
2	51M	V_3–V_6, CM_5, CC_5	2	−	165	645	−/+	Septal-apical	95% LAD	RCA, LCx → LAD
3	48M	V_3–V_6, II, aVF, CM_5, CC_5, CL	2	+	114	405	−/+	Septal	100% LAD	RCA, LCx → LAD
4	40M	V_3–V_6, CM_5, CC_5	4	−	170	660	−/−	—	100% LAD	Diag, LCx → LAD
5	32M	V_4–V_6, III, aVF, CC_5, CM_5, CL	5	+	153	690	−/−	—	90% LAD	RCA → LAD
6	57F	V_5, CM_5	3	+	123	360	−/+	Septal	95% LAD	RCA, LCx → LAD
7	58M	V_5, CC_5, CM_5	2.5	+	158	240	−/−	—	100% LAD	RCA, LCx → LAD
8	56M	V_4, CM_5, CC_5	1	−	167	690	−/−	—	100% LCx	Diag → LCx
9	58M	V_4–V_6, CM_5	1.5	−	172	735	−/−	—	95% RCA	LCx → RCA
10	26F	—	0	−	167	600	−/−	—	100% RCA	LCx → RCA
Group B: Patients With Minimal or No Collateral Vessels										
1	48M	—	0	+	153	720	+/++	Septal-apical	100% LAD	—
2	40M	CM_5	1	+	165	645	−/+	Septal-inf	95% LAD	—
3	62M	V_4–V_6, CM_5, CC_5	2	+	117	180	−/+	Ant-lat, apical	90% LAD	—
4	45M	V_5, CM_5	1	+	147	360	−/+	Septal	90% LAD	—
5	58F	V_5, CM_5	1	+	144	270	+/++	Ant-lat	90% LAD	—
6	57F	V_5, CM_5	2	+	147	525	−/+	Septal	90% LAD	—
7	53F	V_5, CM_5	2	+	167	480	−/+	Septal-apical, inf	90% LAD	—
8	35F	CM_5	1	+	183	580	−/+	Septal	100% LAD	—
9	40F	V_5, CC_5, CM_5	2	+	115	500	−/+	Septal	95% LAD	—
10	49M	V_4–V_6, CC_5, CM_5	4	+	136	630	+/++	Inf-apical	100% LCx	—
11	43M	V_4–V_6, CM_5	1	+	145	600	−/+	Inf-posterior	90% RCA	—
12	33F	V_5, CM_5, CC_5	2	−	177	660	−/+	Ant-lat	95% RCA, Diag	—

Ant = anterior; Diag = diagonal branch of left anterior descending artery; ex = exercise; HR = heart rate; inf = infero; LAD = left anterior descending coronary artery; lat = lateral; LCx = left circumflex coronary artery; Max = maximal; RCA = right coronary artery; S-T↓ = depression; TT = treadmill time.

scintigrams were performed in 22 patients (Table I). Among the 16 patients with left anterior descending arterial stenosis, 81 percent had a positive scintigram compared with 50 percent of the 6 patients with right or left circumflex coronary artery disease (difference not significant). Myocardial perfusion defects were more common in patients without collateral vessels. All 12 patients in group B had perfusion defects compared with only 40 percent (4 of 10) of patients in group A ($p < 0.01$). The extent of hypoperfusion was larger in patients in group B and frequently involved three or more segments ($p < 0.005$) (Table II). The results were similar in patients with occluded coronary arteries and well developed collateral vessels (Fig. 2). The perfusion defect corresponded to the site of coronary artery disease in 94 percent of the 16 patients with a positive scan (Fig. 3).

Discussion

Exercise electrocardiography: The sensitivity of exercise electrocardiography in the detection of coronary artery disease is decreased in patients with single vessel disease (Table III).[1–6,16] The sensitivity ranges from 33 to 95 percent, reflecting the use of differen

TABLE II

Extent of Thallium-201 Perfusion Defect

	No Defect	Two Segments	>Two Segments
Group A (n = 10)	6 (60%)	3 (30%)	1 (10%)
Group B (n = 12)	0 (0%)	5 (42%)	7 (58%)
		$p < 0.005$	

p = probability.

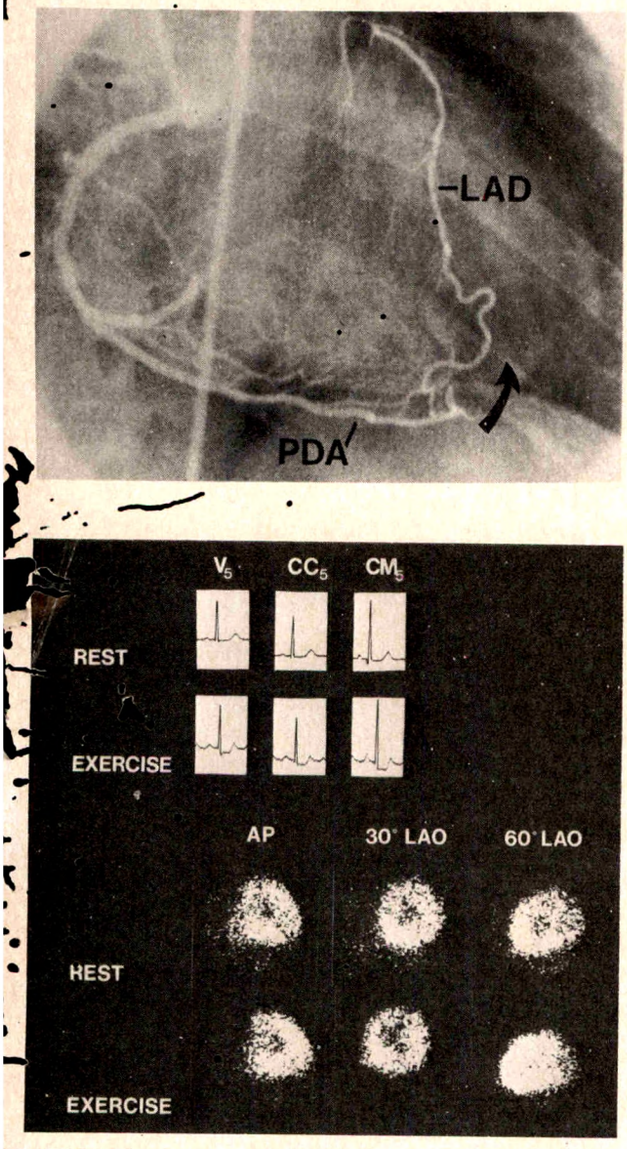

FIGURE 2. Patient 7 (group A). **Top,** contrast injection into the right coronary artery and posterior descending coronary artery (PDA) opacifies the left anterior descending coronary artery (LAD) through large epicardial vessels (**arrow**). **Bottom,** the exercise electrocardiogram shows horizontal S-T segment depression in leads V_5, CC_5 and CM_5; the myocardial scintigrams at rest and during exercise are normal. AP = anteroposterior; LAO = left anterior oblique.

exercise protocols and lead systems, the inclusion of patients with previous myocardial infarction, the location of the diseased vessel and the degree of coronary arterial narrowing required for detection. The higher sensitivity observed in this study results from the presence in all patients of a stenosis of 90 percent or greater of luminal diameter and a normal electrocardiogram and left ventricular contraction pattern at rest.

The sensitivity of exercise electrocardiography was increased in our patients with left anterior descending coronary disease this finding is similar to the results obtained by McHenry et al.[3] but in contrast to the results of other investigators.[4,6] The difference may represent (1) the amount of myocardium that can be rendered potentially ischemic during exercise or (2) the exercise electrocardiographic lead system recorded during and after exercise, or both. A luminal narrowing or less than 75 percent at angiography may not reduce coronary blood flow during exercise by an amount sufficient to show significant differences in the location of the stenosed vessel. Our results suggest that once sufficient muscle has been rendered ischemic to produce an S-T segment shift, the location of the diseased vessel cannot be predicted from the number or location of positive electrocardiographic leads or from the depth of S-T segment depression. Kaplan et al.[6] were also unable to predict the location of single vessel coronary disease in 18 patients who underwent submaximal treadmill tests using leads I, aVF and V_5 or CM_5.[6]

The presence of extensive collateral vessels to the stenosed vessel was not associated with a decreased likelihood of S-T segment depression or an increased work capacity. Similar results have been reported by Martin and McConahay.[2] Thus, extensive collateralization in patients with single vessel disease is not a cause of false negative electrocardiographic results. Decreased sensitivity of the test is related mainly to the degree of coronary arterial narrowing and to the location of the diseased vessel.

Myocardial scintigraphy: The sensitivity of myocardial scintigraphy in detecting single vessel disease (range 43 to 92 percent, Table IV) is greater than that reported for exercise electrocardiography.[7–14] In studies that reported sensitivity according to location of the diseased vessel,[10] perfusion defects were more common when the left anterior descending coronary artery was obstructed. False negative scans were more common in patients with well developed collateral vessels ($p < 0.01$). Similar results were reported by Rigo et al.[18] The patients with large collateral vessels also had smaller perfusion defects than did patients without collateral vessels. Thus, extensive collateralization in patients with single vessel disease is a cause of false negative thallium scans in contrast to exercise electrocardiography, which is largely unaffected by the degree of collateralization.

Limitations of present study: The functional significance of collateral blood vessels in human beings is difficult to evaluate. Several studies have correlated the

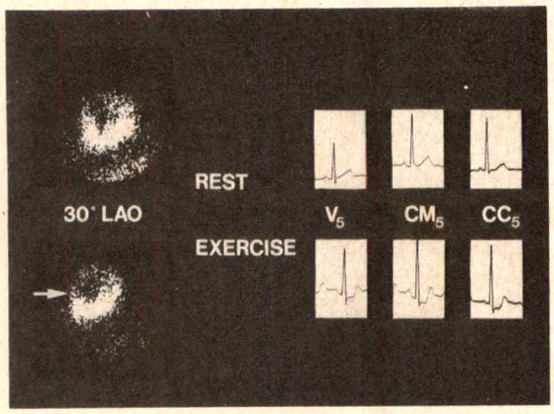

FIGURE 3. Patient 9 (group B). A septal perfusion defect (**arrow**) during exercise is seen in this patient, who had a 95 percent stenosis in the left anterior descending artery and no collateral vessels. The exercise electrocardiogram shows horizontal S-T segment depression in leads V_5, CM_5 and CC_5.

TABLE IV

Reported Sensitivity of Exercise Myocardial Scintigraphy for Single Vessel Disease

First Author	n	Sensitivity (%)	Minimal Degree of Luminal Stenosis (%)
Massie[7]	15	73	70
Lenaers[8]	13	92	50
Bodenheimer[9]	16	56	50
Blood[10]	18	78*	70
McCarthy[11]	30	80	70
Botvinick[12]	8	75	75
Ritchie[13]	46	43	50
Bailey[14]	28	71	70
Present study	22	73†	90

* Sensitivity of 100 percent (7 of 7) for stenosis of left anterior descending artery (LAD), of 86 percent (6 of 7) for stenosis of right coronary artery (RCA), of 25 percent (1 of 4) for stenosis of left circumflex coronary artery (LCx). † Sensitivity of 81 percent (13 of 16) for stenosis of LAD, of 50 percent (2 of 4) for stenosis of RCA and of 50 percent (1 of 2) for stenosis of LCx.

degree of collateralization with wall motion abnormalities and angina but there are few data that correlate the physiologic effects of large collateral vessels visualized on angiography with exercise test results.[20,22–25] Collateral vessels usually become visible when the degree of luminal stenosis exceeds 75 to 90 percent and the collateral channels measure 100 mm or more.[22] Smaller collateral vessels are not visualized with conventional angiographic techniques and consequently could not be assessed in our study. The sensitivity of myocardial scintigraphy for small perfusion defects may be increased with use of the seven pinhole collimator.[26] The radionuclide technique we used in this study is the standard method used in most nuclear medicine laboratories. Collateral blood vessels are more common in patients with multivessel disease[25]; our study group was highly selected. We chose patients with isolated single vessel stenosis of 90 percent or greater to avoid the variable of proximal luminal obstruction that might jeopardize collateral flow and we included no patients with a prior myocardial infarction in order to have a more homogeneous study group. Our results show that collateral vessels can cause false negative thallium scans but do not influence the exercise electrocardiogram. The apparent discrepancy between these two noninvasive tests indicates the importance of the diagnostic approach selected to detect myocardial ischemia.

One possible explanation of this discrepancy is that the coronary collateral circulation can result in nontransmural or subendocardial rather than transmural ischemia. Exercise electrocardiography readily detects subendocardial ischemia, whereas exercise thallium-201 scintigraphy may be more easily defined in the presence of transmural myocardial ischemia. Thus, large collateral vessels may affect the pattern and distribution of myocardial ischemia and both exercise electrocardiography and thallium-201 scintigraphy may reveal different aspects of ischemia.

TABLE III

Reported Sensitivity of the Exercise Electrocardiogram for Single Vessel Disease

First Author	Stenotic Vessel (%)			Total	Lead System	Minimal Degree of Luminal Stenosis (%)
	LAD	RCA	LCx			
Kassebaum[1]	33	50	—	4/8 (50%)	12	50
Martin[2]	—	—	—	8/23 (35%)	12	50
McHenry[3]	92	50	29	19/31 (61%)	CC_5	75
Bartel[4]	38	44	42	20/51 (39%)	12	70
Goldschlager[5]	55	—	—	31/67 (46%)	CS_5	50
Kaplan[6]	53	36	50	18/39 (46%)	1, aVF, V_5/CM_5	50
Present study	95	60	60	30/37 (81%)	12, CC_5, CM_5, CL	90

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

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Lack of Correlation Between Exercise Capacity and Indexes of Resting Left Ventricular Performance in Heart Failure

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Symptoms of congestive heart failure occur most commonly during exercise, but cardiac performance is usually quantitated at rest. The relation between exercise capacity and measurements of cardiac performance at rest is little known. Treadmill exercise was performed in 21 patients with heart failure due to cardiomyopathy. Exercise duration averaged 9.1 ± 0.7 (standard error of the mean) minutes (normal value 12 or more minutes) and did not correlate with resting ejection fraction of 26.4 ± 2.7 percent ($r = -0.06$). Left ventricular diastolic dimension of 6.6 ± 0.2 cm, mean velocity of circumferential fiber shortening and ratio of preejection period to left ventricular ejection time did not correlate with treadmill time ($r = -0.03$). Repeat studies after treatment of heart failure also failed to show correlations between changes in exercise capacity and changes in left ventricular performance at rest. Thus, measures of left ventricular performance obtained at rest do not accurately reflect exercise tolerance and symptomatic status of patients with congestive heart failure.

Patients with congestive heart failure are usually symptomatic during exertion, and it is common clinical practice to estimate their functional capacity and symptomatic status in terms of exercise tolerance.[1] Severity of heart failure is also frequently assessed from measurements of cardiovascular performance obtained at rest, but the relation of these measurements to functional capacity has not been well defined in patients with heart failure. We[2] recently reported that hemodynamic measurements at rest, including left ventricular filling pressure and cardiac output, do not correlate with exercise capacity in patients with chronic left ventricular failure. Because abnormal left ventricular function is thought to be a major cause of impaired exercise capacity in patients with heart failure, and because systemic hemodynamics are affected by factors other than left ventricular performance, it is possible that measures that more closely reflect left ventricular performance would be more predictive of exercise capacity.[3] We therefore performed this study to determine the relations between noninvasively measured indexes of left ventricular function and exercise capacity in ambulatory patients with chronic left ventricular failure.

Methods

Patients: The study group consisted of 21 ambulatory patients aged 38 to 72 years with chronic left ventricular failure who were undergoing baseline evaluation before entry into therapeutic trials with vasodilator drugs. The diagnosis of left ventricular failure was based on a history of exercise intolerance due to dyspnea or fatigue and clinical or radiographic evidence of pulmonary congestion. In addition, patients had to have one of the following: (1) increased heart size by radiologic criteria (cardiothoracic ratio greater than 55 percent); (2) left ventricular diastolic diameter greater than 5.0 cm by echocardiographic examination; and (3) left ventricular ejection fraction below 45 percent by radionuclide or contrast angiography. Symptoms of heart failure must have been present for at least 3 months during treatment with digitalis and diuretic agents.

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The etiology of heart failure was (1) ischemic cardiomyopathy (based on a history of documented acute myocardial infarction or angiographically proved coronary arterial obstructive disease); (2) primary congestive cardiomyopathy (diagnosed when no other cause of heart failure was apparent); or (3) status postvalve replacement (if prosthetic valve function was normal and symptoms of heart failure persisted). Patients were excluded for the following reasons: acute myocardial infarction within the preceding 3 months, primary valvular heart disease, primary pulmonary disease (documented by pulmonary function studies and blood gas determinations), and inability to exercise for reasons other than dyspnea or fatigue.

The clinical characteristics of the patients are shown in Table I. They consisted of 20 men and 1 woman (Case 11), and all were taking digitalis and diuretic drugs. Atrial fibrillation was present in three patients (Cases 3, 7 and 11); the remaining 18 had sinus rhythm.

Measurements of cardiac performance at rest: After giving written informed consent, all patients underwent evaluation of resting left ventricular performance. Diuretic drugs were withheld but digitalis was given on the day of study. No patient had taken a vasodilator drug for at least 2 weeks.

Cardiac output during supine rest was measured noninvasively with the carbon dioxide rebreathing method, an indirect Fick procedure. We have previously validated this noninvasive method in patients with congestive heart failure and found that the results correlated closely with those obtained with the dye-dilution technique.[4,5] Heart rate was measured from a standard electrocardiogram and blood pressure with use of the cuff method.

M mode echocardiograms were obtained with the patient in the supine or left semilateral position, using a Smith-Kline Ekoline Ultrasonoscope and a 2.25 megahertz transducer. The echocardiograms were recorded on a Honeywell direct-writing recorder. Left ventricular end-diastolic and end-systolic dimensions were measured below the tips of the mitral valve leaflets. End-diastole was taken at the peak of the R wave of the electrocardiogram, and end-systole was taken at the shortest distance between septal and posterior walls. External carotid pulse tracings were recorded simultaneously with the echocardiogram, and left ventricular ejection time was measured from the beginning of the upstroke of the carotid pulse to the dicrotic notch. Mean velocity of circumferential fiber shortening was calculated in circumferences per second as the difference between left ventricular end-diastolic and end-systolic dimensions (in cm) divided by the product of left ventricular end-diastolic dimension (in cm) and left ventricular ejection time (in ms).

Systolic time intervals were measured from simultaneous recordings of the external carotid pulse, electrocardiogram and phonocardiogram. The carotid pulse wave was recorded from a brass funnel connected to a Bell and Howell physiologic pressure transducer. The phonocardiogram was recorded from a microphone positioned to record a clear aortic component of the second heart sound (S_2). Electromechanical systole was measured from the onset of the QRS complex to the first high frequency deflection of S_2 ($Q\text{-}S_2$), and left ventricular ejection time (LVET) was measured as described earlier. The preejection period (PEP) was taken as the difference between $Q\text{-}S_2$ and left ventricular ejection time in ms. The ratio PEP/LVET was calculated without correcting for heart rate, which has little effect on this ratio.[6]

Left ventricular ejection fraction was measured with radionuclide imaging techniques using a gated method.[7] The patient's red cells are labeled in vivo with technetium-99m pertechnetate 15 minutes before imaging.[8] Twenty-eight frame multigated studies are obtained over a 5 minute acquisition time and, after background correction, left ventricular ejection fraction is calculated in percent as the difference between end-diastolic and end-systolic counts divided by end-diastolic counts.

Treadmill exercise testing: On completion of all resting measurements, patients underwent upright treadmill exercise testing to a symptom-limited maximum of dyspnea or fatigue using a modified Naughton protocol,[9] which was carried out in the following 2 minute stages: I = 1 miles/hour, 0 percent grade; II = 2 miles/hour, 0 percent grade; III = 2 miles/hour, 3.5 percent grade; IV = 2 miles/hour, 7 percent grade; V = 2 miles/hour, 10.5 percent grade; VI = 3 miles/hour, 7.5 percent grade; VII = 3 miles/hour, 10 percent grade; VIII = 3 miles/hour, 12.5 percent grade; IX = 3 miles/hour, 15 percent grade; and X = 3.5 miles/hour, 14 percent grade. In 14 patients, expired air was continuously collected during exercise and passed on line through gas analyzers for determination of oxygen consumption.

Repeated studies after treatment: These studies at rest and during exercise were repeated in 13 patients 5 weeks after they had been randomly assigned, with a double blind protocol, to therapeutic trials with vasodilator drugs or placebo plus standard treatment with digitalis and diuretic drugs. Because these trials are ongoing, the patients' therapeutic regimens are still unknown. However, for purposes of the present study, the measurements obtained at 5 weeks were analyzed to determine relations between changes in indexes of left ventricular performance at rest and changes in exercise capacity.

The data were analyzed using standard formulas for calculation of mean, standard deviation, standard errors and

TABLE I
Clinical Characteristics of Patients With Chronic Left Ventricular Failure

Case	Age (yr)	Diagnosis	Clinical Class	Duration of Symptoms (mon)	Cardiothoracic ratio (%)
1	52	IHD	III	84	52
2	62	IHD	III	88	57
3	61	PVR	III	60	57
4	59	IHD	III	18	56
5	55	IHD	III	50	59
6	68	IHD	III	80	62
7	57	PVR	III	33	57
8	61	IHD	III	36	52
9	66	IHD	III	19	57
10	62	IHD	III	29	59
11	71	PVR	III	60	66
12	46	PMD	III	78	67
13	57	PMD	IV	60	66
14	38	IHD	III	31	52
15	53	IHD	III	40	55
16	54	IHD	III	11	54
17	50	IHD	III	10	60
18	69	IHD	IV	5	64
19	72	IHD	III	20	59
20	56	IHD	III	24	61
21	46	IHD	III	11	60
Mean	57.9	...	...	40.3	58.7
SEM	1.9	...	...	5.8	1.0

IHD = ischemic heart disease; PMD = primary myocardial disease; /R = post-valve replacement; SEM = standard error of the mean.

coefficients of correlation. Student's paired t test was used to compare values at 5 weeks with control measurements.

Results

Resting left ventricular performance and exercise duration (Table II): Cardiac output and stroke volume could not be obtained in three patients and averaged well below normal for the group. Echocardiographically determined left ventricular end-diastolic dimension and mean velocity of circumferential fiber shortening were also abnormal in 15 patients with satisfactory determinations. The ratio of PEP/LVET was abnormally prolonged in 14 patients. Left ventricular ejection fraction was obtained in all patients and the average was markedly depressed. Exercise duration averaged only 9.1 ± 0.7 minutes in this group of patients. Normal subjects carrying out this same exercise protocol should complete at least 12 minutes.[9] In 14 patients, maximal oxygen uptake averaged 13.7 ± 1.0 ml/kg per min; in our laboratory normal subjects in this age group can achieve greater than 20 ml/kg per min.[2] All exercise tests were stopped because of either dyspnea or fatigue. No one experienced angina or ischemic electrocardiographic changes during exercise. Thus, our patients had significant exercise intolerance accompanied by marked abnormalities of left ventricular performance at rest consistent with significant left ventricular failure.

Correlations between data at rest and exercise performance: The data were analyzed for correlations between indexes of left ventricular performance at rest and exercise duration. Systemic hemodynamic variables did not correlate with exercise duration (r = −0.10 for cardiac output, 0.07 for stroke volume, −0.21 for mean arterial pressure and 0.17 for systemic vascular resistance). Echocardiographically determined left ventricular diastolic dimension did not correlate with exercise duration, and the patient with the smallest dimension had the second shortest exercise duration (Fig. 1). Neither mean velocity of circumferential fiber shortening (Fig. 2) nor the PEP/LVET ratio (Fig. 3) correlated with exercise duration. Left ventricular ejection fraction also failed to correlate with exercise duration (Fig. 4), and the patient with the highest ejection fraction of 63 percent (Patient 11) had one of the shortest exercise durations (4.7 minutes) and the patient with the greatest exercise duration of 17 minutes (Patient 20) had a resting ejection fraction of only 25 percent. Ejection fraction was obtained in the three patients with atrial fibrillation because their ventricular rates were well controlled with only minimal irregularity.

Correlations in repeated studies: The relations between changes in indexes of resting left ventricular performance and changes in exercise capacity were examined in the 13 patients who underwent the same studies after 5 weeks of treatment (Table III). In this subgroup, exercise duration increased significantly by 1.5 ± 0.5 minutes ($p < 0.01$), whereas resting hemodynamic values, echocardiographic variables, PEP/LVET ratio and ejection fraction were not significantly changed after 5 weeks. Likewise, there was no significant correlation between changes in exercise duration and changes in resting indexes of left ventricular performance.

TABLE II

Measures of Left Ventricular Performance at Rest and Exercise Capacity in Patients With Heart Failure

Case	CO (liters/min)	SV (ml/beat)	EDD (cm)	VCF (circ/s)	PEP/LVET	EF (%)	Exercise Duration (min)	VO_2 Max (ml/kg per min)
1	5.0	56	7.0	0.34	0.56	16	8.8	11.9
2	3.4	42	7.7	0.60	0.42	19	10.0	19.0
3	2.9	40	6.3	0.32	0.32	21	8.0	11.1
4	5.7	79	6.9	0.37	0.43	22	10.0	12.1
5	3.0	33	...	...	...	16	6.9	18.9
6	4.1	51	...	...	...	14	6.3	15.8
7	3.5	48	7.2	0.46	0.44	54	10.9	12.8
8	2.5	28	6.6	0.48	0.33	35	10.5	12.5
9	...	...	5.8	0.67	0.40	37	8.0	...
10	2.5	25	6.6	0.53	...	31	10.5	12.6
11	...	...	4.5	0.71	0.31	63	4.7	...
12	4.7	52	7.8	0.23	0.44	24	9.9	13.2
13	3.9	50	7.3	0.32	0.55	21	3.4	5.6
14	4.0	50	5.7	0.61	0.39	21	11.0	16.6
15	5.0	84	6.9	0.74	0.35	23	10.0	17.9
16	3.3	45	5.8	0.53	0.23	12	10.0	11.4
17	3.9	42	...	...	...	25	10.9	...
18	4.6	50	...	...	...	23	2.7	...
19	3.9	54	6.8	0.54	0.35	33	10.0	...
20	...	...	...	...	...	25	17.0	...
21	4.1	64	...	...	...	19	11.6	...
Mean	3.9	49.6	6.6	0.50	0.43	26.4	9.1	13.7
SEM	0.2	3.6	0.2	0.04	0.05	2.7	0.7	1.0

CO = cardiac output; EDD = left ventricular end-diastolic dimension; EF = left ventricular ejection fraction: PEP/LVET = ratio of preejection period to left ventricular ejection time; SEM = standard error of the mean. SV = stroke volume; VCF = mean velocity of circumferential fiber shortening; VO_2 Max = maximal oxygen consumption.

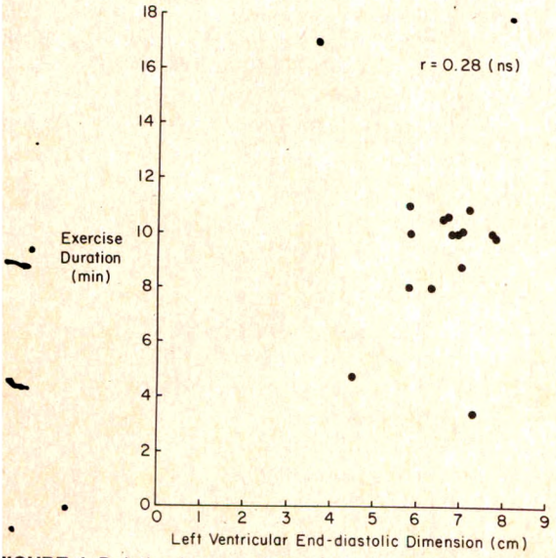

FIGURE 1. Relation between left ventricular end-diastolic dimension on echocardiography and exercise capacity in patients with heart failure.

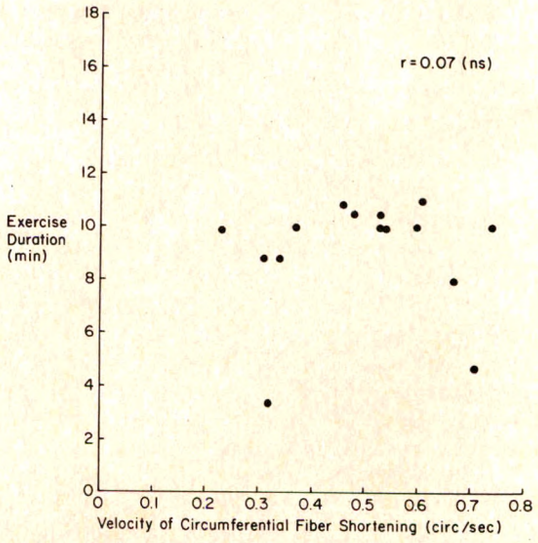

FIGURE 2. Relation between left ventricular mean velocity of circumferential fiber shortening (on echocardiography) and exercise capacity in patients with heart failure.

Discussion

Correlation of clinical symptoms, exercise capacity and left ventricular performance: In the absence of impaired ventilatory function, skeletal muscle abnormalities or inability of blood to carry adequate amounts of oxygen, cardiovascular performance becomes the major determinant of exercise capacity. Therefore, patients with heart failure are usually limited in their capacity to exercise, presumably because impaired left ventricular performance has led to an excessive increase in pulmonary capillary pressure and premature dyspnea or inadequate cardiac output and early muscle fatigue.[3,10] It is common clinical practice to estimate the severity of heart failure symptoms by relating them to their precipitating physical activities.[1] However, when such clinical classifications are compared with actual quantitation of exercise capacity in patients with heart failure, the correlation is not very good.[2,9] Measurements of cardiovascular performance

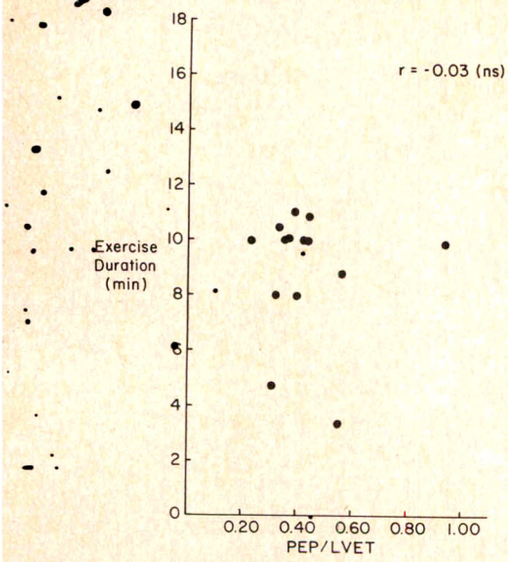

FIGURE 3. Relation between systolic time intervals (preejection period [PEP] and left ventricular ejection time [LVET]) and exercise capacity in patients with heart failure.

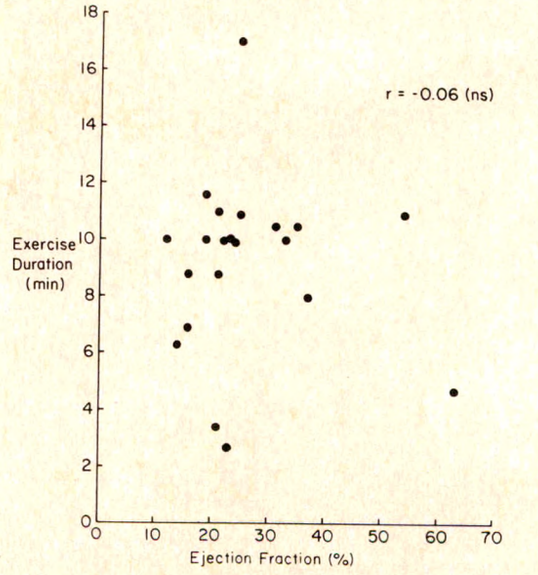

FIGURE 4. Relation between left ventricular ejection fraction (on nuclear angiography) and exercise capacity in patients with heart failure.

TABLE III

Changes in Exercise Capacity and Resting Left Ventricular Performance in Patients With Heart Failure (changes from control in repeated tests)

Case	Exercise Duration (min)	CO (liters/min)	SV (ml/beat)	EDD (cm)	VCF (circ/s)	PEP/LVET	EF (%)
3	4.0	0.1	−7	−0.1	0.58	0.22	12
4	2.0	−3.0	−40	−0.2	−0.10	0.00	11
6	4.6	0.9	10	...	...	...	0
7	1.0	1.2	14	−1.8	0.42	−0.12	13
8	1.2	1.6	23	0.8	0.21	0.33	−4
9	0.3	...	...	−0.1	−0.19	−0.02	−7
10	1.0	...	...	−0.1	−0.22	0.07	...
11	1.1	0.2	7	0.0	−0.14	...	−1
12	0.8	...	...	...	...	...	4
13	2.8	0.5	4	0.4	0.23	−0.50	10
14	0.2	0.1	2	−1.3	−0.09	−0.13	0
16	1.7	−0.5	−14	−0.8	0.09	0.13	2
19	−1.6	−2.0	−22	0.0	0.31	−0.45	−5
n	13	10	10	11	11	10	12
Mean	1.5	−0.1	−2.3	−0.3	0.10	−0.05	2.9
SEM	0.5	0.5	5.9	0.2	0.08	0.08	2.0
p*	<0.01	NS	NS	NS	NS	NS	NS
r†	...	0.31	0.16	0.16	0.33	0.40	0.50

* Probability value compared with control (see Table II for individual control values). † Coefficient of correlation with change in exercise duration.

CO = cardiac output; EF = left ventricular ejection fraction; n = number of studies; NS = not significant; PEP/LVET = ratio of preejection period to left ventricular ejection time; SEM = standard error of the mean; SV = stroke volume; VCF = velocity of circumferential fiber shortening.

at rest are also frequently used to assess the severity of heart failure. Although these measurements often provide useful information to help guide short-term therapeutic interventions and may also be of prognostic value in predicting length of survival, their relation to symptomatic severity and functional capacity is not well established.[11] Recent therapeutic trials[12,13] have shown that acute improvement in left ventricular performance is not associated with increased exercise tolerance in patients with left ventricular failure. Conversely, other studies[14,15] in similar patients have demonstrated improved exercise capacity during long-term therapeutic interventions that were not associated with significant changes in indexes of left ventricular performance at rest.

We recently reported that resting hemodynamic measurements, including left ventricular filling pressure and cardiac output, although markedly abnormal in patients with impaired exercise tolerance and heart failure, did not separate groups with varying severity of exercise intolerance. We found no correlations between resting left ventricular filling pressure, cardiac output, stroke volume or systemic vascular resistance and maximal oxygen uptake. However, these hemodynamic measurements are determined by factors other than left ventricular function. Systemic vascular resistance through its effects on impedance is a major determinant of output of the failing ventricle and, because resistance decreases greatly during exercise, cardiac output at rest may not reflect what happens during exercise.[3,16] Left ventricular filling pressure, besides being influenced by diastolic characteristics of the left ventricle, is also a function of intravascular volume and left ventricular outflow resistance.[17]

Left ventricular performance at rest for predicting exercise capacity: Thus, the present study was intended to assess the relation of exercise capacity to more direct measures of left ventricular function. Although assessment of myocardial contractility of the intact heart is notoriously difficult, the noninvasive measures used in this study are all thought to reflect left ventricular performance to some degree. Left ventricular diastolic dimension and mean velocity of circumferential fiber shortening are both believed to be indicators of contractile function.[18] Of course, use of these echocardiographic measurements in the present study involving predominantly patients with ischemic heart disease may be questioned because of the spatial limitations of M mode echocardiography and geometric asymmetry of the left ventricle in such patients.[19] Left ventricular ejection fraction is a widely used measure of contractile function and, when measured with blood pool imaging methods, is a reliable index and not affected by ventricular geometry.[20–22] Likewise, systolic time intervals, especially the PEP/LVET ratio, are thought to reflect contractility independent of ventricular geometry and, in some studies, PEP/LVET has correlated closely with ejection fraction.[6] All of these ejection phase indexes were found to be markedly abnormal and consistent with moderately severe left ventricular dysfunction and failure in the present study. Our patients also had very limited exercise capacity, but within this group of incapacitated patients, we found no correlations between exercise capacity and the measures of left ventricular performance at rest. These results are similar to those of Benge et al.[23] who also found no correlation between ejection fraction at rest and exercise capacity in cardiac patients.

Our observations were also repeated after treatment of heart failure and, although exercise duration was increased, measures of ventricular performance at rest were unchanged. Furthermore, there were no correlations between changes in resting ejection phase indexes and changes in exercise capacity. Thus, knowledge of resting indexes of left ventricular performance is not predictive of exercise capacity in patients with chronic left ventricular failure; also, changes in ventricular performance at rest do not appear to be useful for following changes in functional capacity of such patients. In fact, Lee et al.[24] recently noted improved exercise capacity without changes in left ventricular function after training in patients with coronary artery disease and a low ejection fraction.

These results should not be too surprising because exercise itself may produce marked changes in left ventricular performance. Heart rate increases strikingly and is the major contributor to increasing cardiac output. Contractility may increase as a result of increased preload or catecholamine release, or both. Preload and ejection fraction are variably altered, and impedance would be expected to decrease as a result of decreased systemic vascular resistance, which may, however, be offset by the increase in systolic blood pressure and the vasoconstriction in nonexercising vascular beds.[3,25] The net effects of the interplay of all these factors can not be predicted from knowledge of their resting state. It is quite likely that hemodynamic responses and changes in ventricular performance during exercise are major determinants of exercise capacity in patients with heart failure.[26]

Possible limitations of study: This study is weakened by a lack of similar data in normal subjects or subjects with mild cardiac disease, and our results are applicable only to patients with limited exercise capacity and impaired cardiac function. Furthermore, we have studied only patients who were limited by symptoms of heart failure and excluded those limited by myocardial ischemia. The exercise protocol employed is also subject to criticism. Patients were not previously familiarized with the exercise testing procedure, but we have previously observed no significant variation between results obtained from successive tests at 90 minute intervals in patients with heart failure.[2,12–24] The use of 2 minute stages might also be questioned, but we have previously reported that maximal oxygen uptake achieved with the present protocol is the same as that achieved during a bicycle exercise test employing 4 minute stages in the same patients.[2] The maximal oxygen uptake occurs at a time when the ventilatory exchange ratio is elevated, indicating onset of anaerobic metabolism and achievement of maximal or very near maximal stress.[2,12–14]

Implications: Our study confirms previous observations that hemodynamic measurements at rest are not predictive of exercise capacity in patients with left ventricular failure. It also establishes that more direct measures of left ventricular performance likewise fail to correlate with exercise capacity in these patients. Therefore, exercise testing is preferred in order to assess functional capacity of patients with heart failure. Evaluation of the many new interventions for heart failure should not focus solely on hemodynamic effects or changes in ventricular performance as the primary goal, but should include exercise testing to monitor patient progress and judge therapeutic efficacy. Although ejection phase indexes of myocardial contractility are of prognostic value,[22,27] exercise testing may be preferable in evaluating quality of life, which could be favorably altered without necessarily improving cardiac performance or longevity.

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Systolic and Diastolic Properties of the Human Left Ventricle During Valve Replacement for Chronic Mitral Regurgitation

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M mode and two dimensional echocardiography were combined with pressure-flow data to analyze systolic mechanics and diastolic compliance in nine patients during valve replacement for chronic mitral regurgitation. Both M mode (six patients) and two dimensional (four patients) echographic analyses revealed large decreases in early postoperative shortening fraction (-24 ± 17 [standard deviation] percent M mode study, $p < 0.01$; -30 ± 12 percent two dimensional study, $p < 0.02$), which were significantly different from small changes observed in control subjects (M mode study, $+7 \pm 10$ percent, 25 subjects and two dimensional study, -7 ± 14 percent, 8 subjects). Additional data suggest that left ventricular compliance is increased in chronic mitral regurgitation and that elimination of the low impedance left atrial pathway by valve replacement is associated with a significant increase in wall stress (five patients, $p < 0.02$) that appears to be responsible for the decreased ejection fraction postoperatively. Analysis of hemodynamic variables other than ejection fraction and rate of circumferential shortening revealed no difference between five postoperative patients with chronic mitral regurgitation and five with coronary artery disease. These results in human subjects confirm predictions from studies in animal models and suggest that unique properties of chronic mitral regurgitation demand special attention when patients with this condition are being evaluated for surgery.

The clinical course of chronic mitral regurgitation is typically one of slow progression over many years with late development of symptoms.[1–5] Indications for valve replacement are traditionally based on the development of these symptoms.[6] Despite the apparent slow progression and often comparatively favorable medical assessment of hemodynamic status, patients undergoing valve replacement for chronic mitral regurgitation have higher postoperative morbidity and mortality rates with greater depression of hemodynamic performance than have patients undergoing surgery for mitral stenosis or most other adult cardiac lesions.[6–16] This depression of ventricular performance in chronic mitral regurgitation is manifested as depressed postoperative ejection fraction and has been shown to persist on long-term follow-up study.[8,17–18]

Animal models of acute and chronic mitral regurgitation have demonstrated an increase in afterload after reversal of the lesion.[4,19–20] This finding suggests that valve replacement for chronic mitral regurgitation exposes pathologic depression of left ventricular performance that is not readily apparent preoperatively and that leads to an adverse postoperative outcome.[19] The direct effect of valve replacement on left ventricular function and systolic mechanics in patients with chronic mitral regurgitation has not been demonstrated. The purpose of this study, therefore, is to utilize intraoperative measurements of hemodynamic function,

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ventricular compliance and systolic mechanics to demonstrate properties unique to chronic mitral regurgitation that would serve to identify these patients as a distinct group requiring special attention.

Methods

Patients: Left ventricular properties were studied intraoperatively at the time of cardiac surgery in 9 patients with predominant chronic mitral regurgitation and compared with findings in a general population of 33 patients undergoing open heart surgery for a condition other than chronic mitral regurgitation. Measurements were obtained intraoperatively before and after completion of cardiopulmonary bypass. The withdrawal and infusion of blood that normally accompany the use of the heart-lung machine provided a natural physiologic laboratory to complete our studies. Informed consent was obtained before surgery. There were no study-related complications.

Pressure-flow data: To obtain pressure and flow data, a Millar Mikro-tip velocity/pressure transducer catheter (VPC-663A, Millar Instruments Inc., Houston, Texas) was inserted through an injection site in the ascending aorta, and the pressure sensor was positioned in the left ventricular cavity. A high frequency differentiator was used to provide the first derivative of left ventricular pressure (dP/dt) (Cardiac Contractility Computer SB-20B, Crane Bio-Medical Instruments, Inc., Elmont, New York). Flow data for systolic mechanics were provided by an electromagnetic flow velocity probe, 2 cm proximal to the catheter tip, positioned just above the aortic valve. A Swan-Ganz thermodilution catheter (Edwards Laboratories, Santa Ana, California) was placed in the main pulmonary artery. Pressure-flow data for left ventricular mechanics were obtained simultaneously with thermodilution determinations of cardiac output to calibrate the flow-velocity probe. Radial arterial pressures were recorded using a percutaneous Teflon® catheter and fluid-coupled pressure transducer. The opening and closing of the aortic valve could be determined from simultaneous left ventricular and radial arterial pressures after correction for the time delay in the radial arterial pressure (Fig. 1).

M mode echocardiography: A 3.5 megahertz low profile M mode echographic transducer (Aerotech Laboratories, Lewistown, Pennsylvania) imbedded in a Silastic® disc for stability was inserted into the posterior pericardium in a retrocardiac position. This technique did not cause interference with surgery. Echographic data (ECT Echocardiotrace, Metrix, Inc., Denver, Colorado) and pressure-flow data for left ventricular mechanics were recorded with an optical oscillograph equipped to record M mode echocardiograms and standard analog data signals (1858 CRT Visicorder, Honeywell, Inc., Denver, Colorado). This method has previously been described.[21,22] Left ventricular end-diastolic and end-systolic diameters were obtained from the M mode echocardiogram. The end-diastolic diameter was measured from the top of the R wave of the simultaneously occurring electrocardiogram. The end-systolic diameter was measured at the point where the opposing ventricular walls most closely approximated each other.

Two dimensional echocardiography: In selected patients, evaluation of left ventricular performance was based on changes in the short axis cross section measured with two dimensional phased array echocardiography. A gas-sterilized 3.5 megahertz two dimensional echographic transducer (Varian V-3000 Electronic Phased Array Ultrasonograph, Varian, Palo Alto, California) was placed against the anterior surface of the right ventricle to obtain cross sections at the level of the tip of the mitral valve leaflets. Quantitative analysis of the video images obtained was performed using the V-3000 Microprocessor Controlled Light Pen. The end-diastolic area was determined with planimetry from the video image synchronous with the peak of the R wave of the electrocardiogram. The end-systolic area was chosen as the smallest area determined with planimetry during systole.

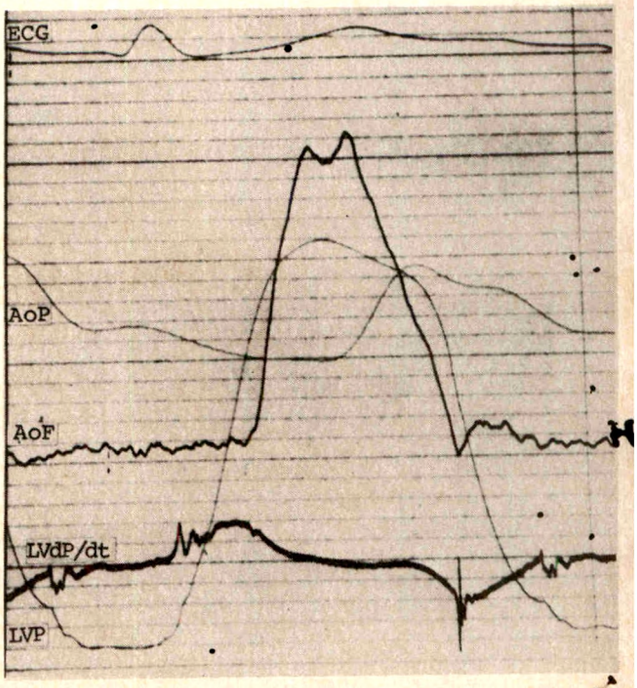

FIGURE 1. Patient 4. Representative intraoperative data recording after cardiopulmonary bypass and valve replacement for chronic mitral regurgitation. Aortic pressure (AoP) is measured from a radial arterial catheter and contains an appropriate time delay in recording of the tracing. AoF = aortic flow; ECG = electrocardiogram; LVdP/dt = first derivative of left ventricular pressure; LVP = left ventricular pressure.

Protocol for data acquisition: All studies were performed after aortic cannulation for cardiopulmonary bypass as a safeguard against hypotension or arrhythmias during the studies. However, no such problems were observed. Catheters were inserted after heparinization and removed before administration of protamine. The order of instrumentation when all studies were performed was catheter insertion, two dimensional echocardiography and M mode echocardiography. Studies were conducted in reverse order after cardiopulmonary bypass. The presence of pericardial adhesions was a contraindication to M mode echocardiography from the retrocardiac position. The presence of valve vegetations was a contraindication to catheter placement. Two dimensional echocardiographic equipment was not available for early studies.

Of the total of nine patients with chronic mitral regurgitation, five had complete studies of left ventricular mechanics, four had satisfactory studies of left ventricular compliance (pressure-diameter data), six had M mode studies of shortening fraction, and four had two dimensional echographic

TABLE I

Left Ventricular Properties in Five Patients With Chronic Mitral Regurgitation

Case	Age (yr) & Sex	Functional Class*	Angiographic Measurements				Intraoperative Measurements Before Valve Replacement		
			Mass (g)	EDP (mm Hg)	EDV (ml)	EF (%)	EDP (mm Hg)	EDV (ml)	EF (%)
1	71F	IV†	705	15	637	77	9	511	76
2	64M	III	584	12	340	42	6	249	55
3	40F	III	244	16	216	55	7	92	48
4	59F	III	415	12	301	47	8	231	61
5	26M	IV‡	658	9	690	—	17	579	50

*Functional class as indicated in: Bruce RA. Evaluation of functional capacity and exercise tolerance of cardiac patients. Med Concepts Cardiovasc Dis 1956;25:321–6. Etiology rheumatic, except as noted. † Ruptured chordae superimposed on chronic mitral regurgitation. ‡ Etiology myxomatous degeneration plus history of endocarditis. EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction.

studies of ejection fraction. Similar constraints applied to the control group.

Angiographic data: Cardiac catheterization was performed as part of the preoperative evaluation in all patients. End-diastolic volume, ejection fraction and left ventricular mass were obtained from the contrast cineventriculogram taken in the standard right anterior oblique view (Table I). Quantitative analysis was based on the single plane area-length method.[23–25] Comparison of left ventricular end-diastolic pressure during angiography with observations in the open chest was facilitated by assuming an intrapleural pressure of −7 mm Hg during angiography and adding this value to left ventricular end-diastolic pressure to obtain effective transmural pressure.

Calculations

Compliance curves: Left ventricular end-diastolic pressure was plotted against left ventricular end-diastolic diameter as a measure of diastolic compliance.[21,22,26] Pressure was obtained directly from the indwelling micromanometer, and end-diastolic diameter (EDD) was obtained from the retrocardiac M mode echocardiogram. Echocardiographically determined volume ($V = EDD^3$)[27–29] intraoperatively was related to the preoperative angiographically determined volumes (single plane area-length method) with use of a nomogram that has a correlation coefficient of 0.82 in our laboratory (Fig. 2). Data were analyzed by an exponential curve fitting to the relation: $EDD = ae^{bEDD}$ where the constants a and b were averaged for statistical comparisons.

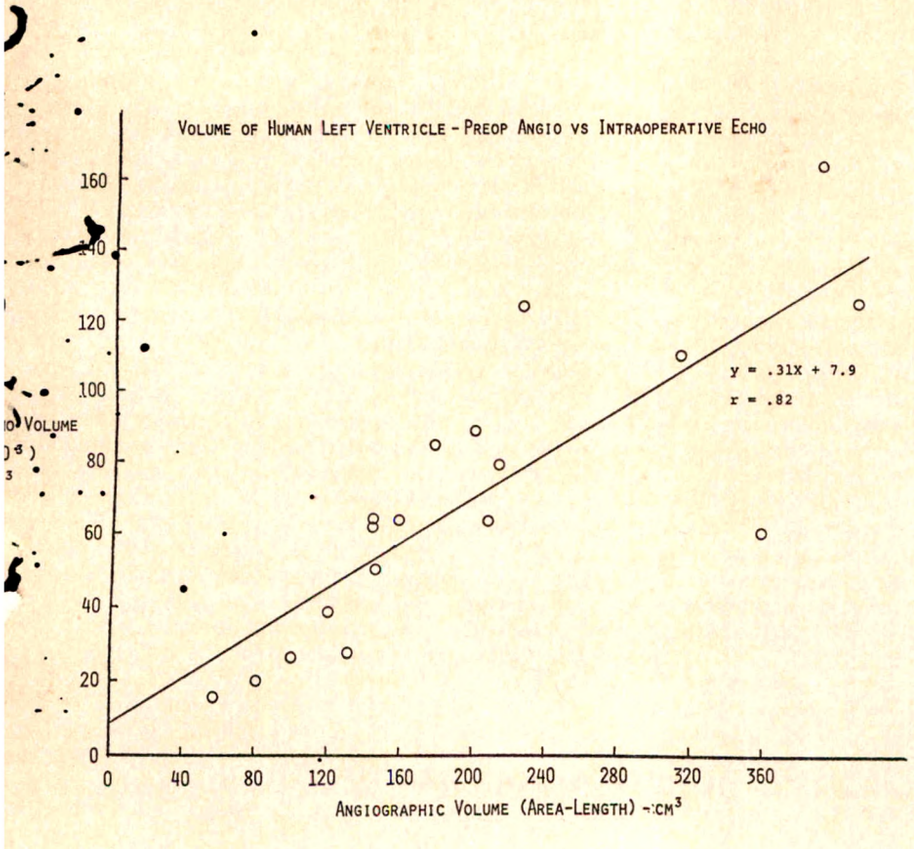

FIGURE 2. Linear regression for the relation of angiographically determined left ventricular volume to intraoperative measurements (D^3) by M mode echocardiography. The regression formula is illustrated.

Ejection fraction: Measurements of left ventricular dimensions with M mode (left ventricular diameter) and two dimensional (left ventricular cross-sectional area) echocardiography were treated similarly to obtain fractional changes during systole. For M mode data, shortening fraction (SF) was defined as SF = (EDD − ESD)/EDD, where EDD and ESD are end-diastolic and end-systolic diameter, respectively. For two dimensional short axis images, ejection fraction (EF) was defined as EF = (EDA − ESA)/EDA where EDA and ESA are end-diastolic and end-systolic area, respectively. No patients with focal wall motion abnormalities with the exception of paradoxical septal motion, were included in our two dimensional studies.

Systolic mechanics: Left ventricular pressure, aortic flow and dP/dt were measured at 20 ms intervals and entered into a PDP-11/70 computer for calculation of variables of systolic mechanics using a changing volume spherical model.[30] Left ventricular volume (V) is given by V = end-diastolic volume − SV, where end-diastolic volume is obtained from end-diastolic diameter and the nomogram, and SV is instantaneous stroke volume from the flow-velocity curve, calibrated by simultaneous thermodilution stroke volume. Instantaneous chamber radius (Ri) is then given by $Ri = (0.239\ V)^{1/3}$. Similarly, external radius (Ro) of the spherical "ventricle" is given by $Ro = (0.239[V + M])^{1/3}$, where M = left ventricular mass, determined angiographically. Left ventricular wall stress is calculated as wall stress = $\pi PRi^2/(Ro^2 - Ri^2)$ where P = left ventricular pressure, Ri = internal radius and Ro = external radius.[30]

The calculation of the velocity of contractile element shortening (*Vce*) is based on the two component model for cardiac muscle where a contractile element is linked in series to a series elastic element.[31,32] Vce is equal to the sum of the velocity of circumferential shortening (Vcf) and the velocity of the series elastic element elongation (Vse). It has been shown that Vcf (cm/s) = Q (cm^3/s)/2RoRi (cm^2), where Q = instantaneous flow out of the ventricle.[20,33] The velocity of series elastic element elongation is determined from the equation Vse = (dT/dt)/KT where T = wall tension (g/cm^2) and KT = the modulus of elasticity of the series elastic component of muscle.[30,32] The normalized value for K used in this study is 28.6, a value based on observations on the isolated heart muscle.[32,34]

Ventricular volume during mitral regurgitation required estimation of the regurgitant fraction in addition to the stroke volume directly recorded by the aortic flow probe. To solve this problem, total ejection volume was determined by subtracting the end-systolic from the end-diastolic volume. Both volumes were obtained from M mode measurements of end-systolic and end-diastolic diameters and related to angiographically determined volumes through the nomogram discussed earlier (Table I). The measured aortic flow was then calibrated by setting the integrated stroke volume equal to the total ejection volume, assuming equal rates of ejection into the aorta and left atrium. Instantaneous volume was obtained by subtracting the newly calibrated aortic flow (calibrated to equal ejection volume) from the end-diastolic volume.

Statistical tests: Simple statistics were done with a programmed hand calculator (S-61, Commodore). Mean values for simple hemodynamic variables in different populations were compared with unpaired *t* tests (see Fig. 4 and 5, Table III). Changes within a single population were compared by paired *t* test (Table II). Significance of differences between exponentials fitted to compliance curves was tested with an unpaired *t* test applied to the base and exponential constants.

TABLE II

Integral of Systolic Wall Stress (g/cm^2) After Mitral Valve Replacement in Five Patients

Case	Preoperative	Postoperative
1	18.9	31.1
2	29.0	30.3
3	19.9	31.8
4	28.8	43.4
5	33.0	43.4
Mean*	25.9 ± 6.2	36.0 ± 6.8

* $p < 0.02$, paired *t* test, preoperatively versus postoperatively.

Results

Diastolic pressure-diameter relations: Average end-diastolic pressure-diameter curves for four patients with chronic mitral regurgitation and three patients with mitral stenosis are illustrated in Figure 3. The exponential equation derived for mitral stenosis (line B) is: $EDP = (0.09 \pm 0.02)e^{(1.45\pm0.17)\ EDD}$, where EDP = left ventricular end-diastolic pressure and EDD = left ventricular end-diastolic diameter. The exponential equation derived for chronic mitral regurgitation (line A) is: $EDP = (0.52 \pm 0.35)e^{(0.72\pm0.18)EDD}$. The curve representing chronic mitral regurgitation is shifted to the right and the slope is decreased at any given end-diastolic pressure compared with the pressure curve representing mitral stenosis. However, observed differences in the base and exponential constants of the derived regressions are not statistically significant.

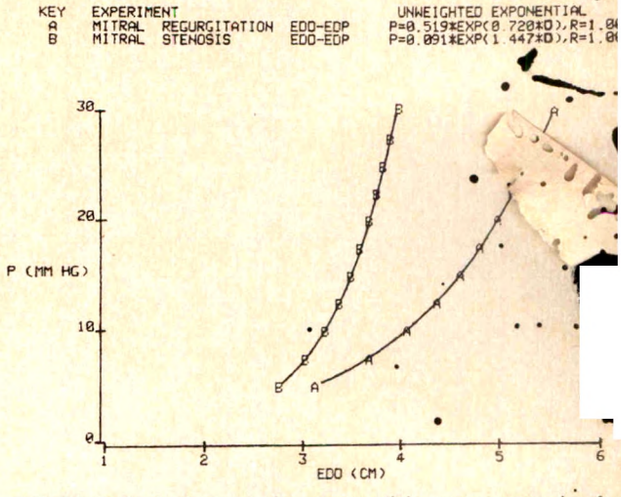

FIGURE 3. Derived composite exponential curves comparing four patients with chronic mitral regurgitation (A) and three patients with mitral stenosis (B). P = pressure. Chronic mitral regurgitation is associated with an increase in left ventricular compliance characterized by a shift of the curve to the right and by decreased slope at any given left ventricular end-diastolic pressure. EDD = end-diastolic diameter; EDP = end-diastolic pressure.

Shortening fraction: Preoperative and postoperative M mode shortening fractions for 6 patients with chronic mitral regurgitation and 25 control patients are illustrated in Figure 4. The control group consisted of 11 patients undergoing coronary revascularization, 5 having aortic valve replacement, 5 having mitral valve replacement for mitral stenosis, 3 undergoing closure of secundum type atrial septal defect and 1 patient undergoing correction of congenital pulmonary stenosis. The control group showed an average 7 ± 10 percent increase in postoperative M mode shortening fraction from 27 ± 15 to 34 ± 15 percent ($p < 0.01$, paired t test). The patients with chronic mitral regurgitation showed a 24 ± 17 percent decrease in postoperative M mode shortening fraction from 37 ± 12 to 13 ± 10 percent ($p < 0.01$, paired t test). The decrease in postoperative M mode shortening fraction seen in the group with chronic mitral regurgitation was statistically significant ($p < 0.001$, unpaired t test) compared with the increase in the postoperative M mode shortening fraction seen among the control group.

Preoperative and postoperative two dimensional "ejection fraction" (Fig. 5) were compared in four patients with chronic mitral regurgitation and eight control subjects, including three patients undergoing aortic valve replacement, three undergoing mitral valve replacement for mitral stenosis, one patient undergoing coronary revascularization and one undergoing triple valve replacement for bacterial endocarditis. The control subjects showed an average 7 ± 14 percent decrease

TABLE III

Postoperative Left Ventricular Mechanics in Five Patients With Chronic Mitral Regurgitation and Five With Coronary Artery Disease

	Mitral Regurgitation (valve replacement)	Coronary Artery Disease (bypass grafting)
EDV angio (ml)*	437 ± 213	128 ± 33
Mass (g)*	521 ± 190	195 ± 42
r/h at peak wall stress	2.7 ± 0.3	2.3 ± 0.8
LVEDP (mm Hg)	9 ± 3	9 ± 3
Peak LVP (mm Hg)	99 ± 9	90 ± 14
Time to peak (ms)	260 ± 32	220 ± 37
Stroke volume (ml)	51 ± 12	44 ± 16
Peak Ao flow (ml/s)	274 ± 81	260 ± 60
Time to peak (ms)	236 ± 55	208 ± 48
TTI (g-s/cm^2)	42 ± 4	41 ± 8
PVSW (g-m)	64 ± 13	53 ± 21
Peak stress (g/cm^2)	119 ± 22	106 ± 39
Integral stress (g/cm^2)	36 ± 7	31 ± 16
VCf (circ/s)*	0.21 ± 0.08	0.46 ± 0.18
VCe (cm/s)	18 ± 5	15 ± 2
Peak dP/dt (mm Hg/s)	927 ± 182	1102 ± 525
Time to peak (ms)	72 ± 27	88 ± 36

* $p < 0.02$, unpaired t test, mitral regurgitation versus coronary artery disease.

Ao flow = aortic flow; circ = circumference; dp/dt = first derivative of left ventricular pressure; EDV = end-diastolic volume; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular pressure; PVSW = pressure-volume stroke work; r/h = radius/wall thickness; TTI = tension-time index; VCe = velocity of contractile element shortening; VCf = velocity of fiber shortening.

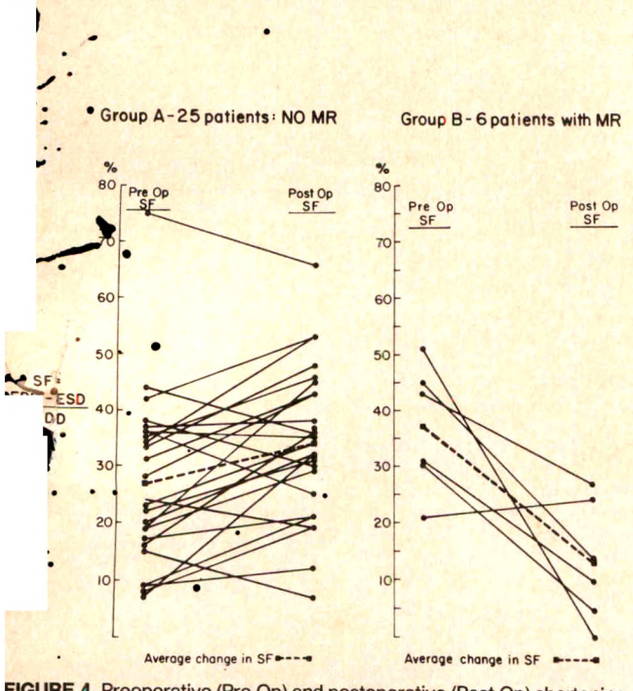

FIGURE 4. Preoperative (Pre Op) and postoperative (Post Op) shortening fractions (SF) compared in 25 patients with no mitral regurgitation (MR) (Group A) and 6 patients with chronic mitral regurgitation (Group B). The **dashed lines** represent the average change in SF. Shortening fraction increases significantly in Group A and decreases significantly in Group B ($p < 0.001$, unpaired t test compared with the rise in Group A).

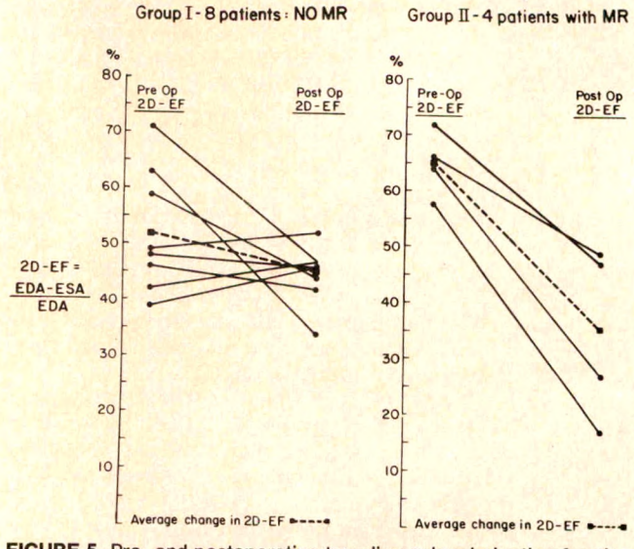

FIGURE 5. Pre- and postoperative two dimensional ejection fraction (2D-EF) compared between Group I consisting of eight patients with no mitral regurgitation and Group II consisting of four patients undergoing valve replacement for chronic mitral regurgitation. The **dashed lines** represent the average change in 2D-EF. A small decrease in postoperative shortening fraction in Group I is not statistically significant. Shortening fraction in Group II is significantly decreased postoperatively ($p < 0.02$, unpaired t test compared with that in Group I). EDA = the planimetered end-diastolic area; ESA = the planimetered end-systolic area.

in postoperative two dimensional "ejection fraction" from 52 ± 11 to 45 ± 6 percent, which was not statistically significant ($p < 0.10$, paired t test). The patients with chronic mitral regurgitation showed an average 30 ± 12 percent decrease in postoperative two dimensional "ejection fraction" from 65 ± 6 to 35 ± 16 percent ($p < 0.02$, paired t test). The greater decrease in postoperative two dimensional "ejection fraction" in the group with chronic mitral regurgitation compared with that in the control group was statistically significant ($p < 0.02$, unpaired t test).

Left ventricular mechanics: The time course of selected variables of left ventricular performance in chronic mitral regurgitation immediately before and after valve replacement is presented in Figure 6. Illustrated are left ventricular pressure, radius, wall thickness and wall stress at equivalent left ventricular end-diastolic pressures. Postoperatively, there is an increase in systolic pressure and wall stress during the latter part of systole. Systolic shortening is decreased, and less change in radius is apparent. There is a decrease in the extent of wall thickening. Differences are maximal late in systole, reflecting decreased changes in left ventricular volume with systole after correction of chronic mitral regurgitation.

The time course of preoperative and postoperative wall stress in the five patients with chronic mitral regurgitation studied is illustrated in Figure 7. The integrals of these wall stress curves (Table II) are increased in all five patients after valve replacement. The average increase from 25.9 ± 6.2 to 36.0 ± 0.8 g/cm^2 is statistically significant ($p < 0.02$, paired t test).

Comparison with coronary disease: Table III compares average postoperative left ventricular mechanics in five patients with chronic mitral regurgitation and five patients undergoing revascularization for coronary artery disease. Left ventricular volume and mass were significantly increased in the patients with chronic mitral regurgitation ($p < 0.02$) and velocity of circumferential fiber shortening at peak wall stress was significantly decreased in this group. Other calculated variables of left ventricular performance were not sig-

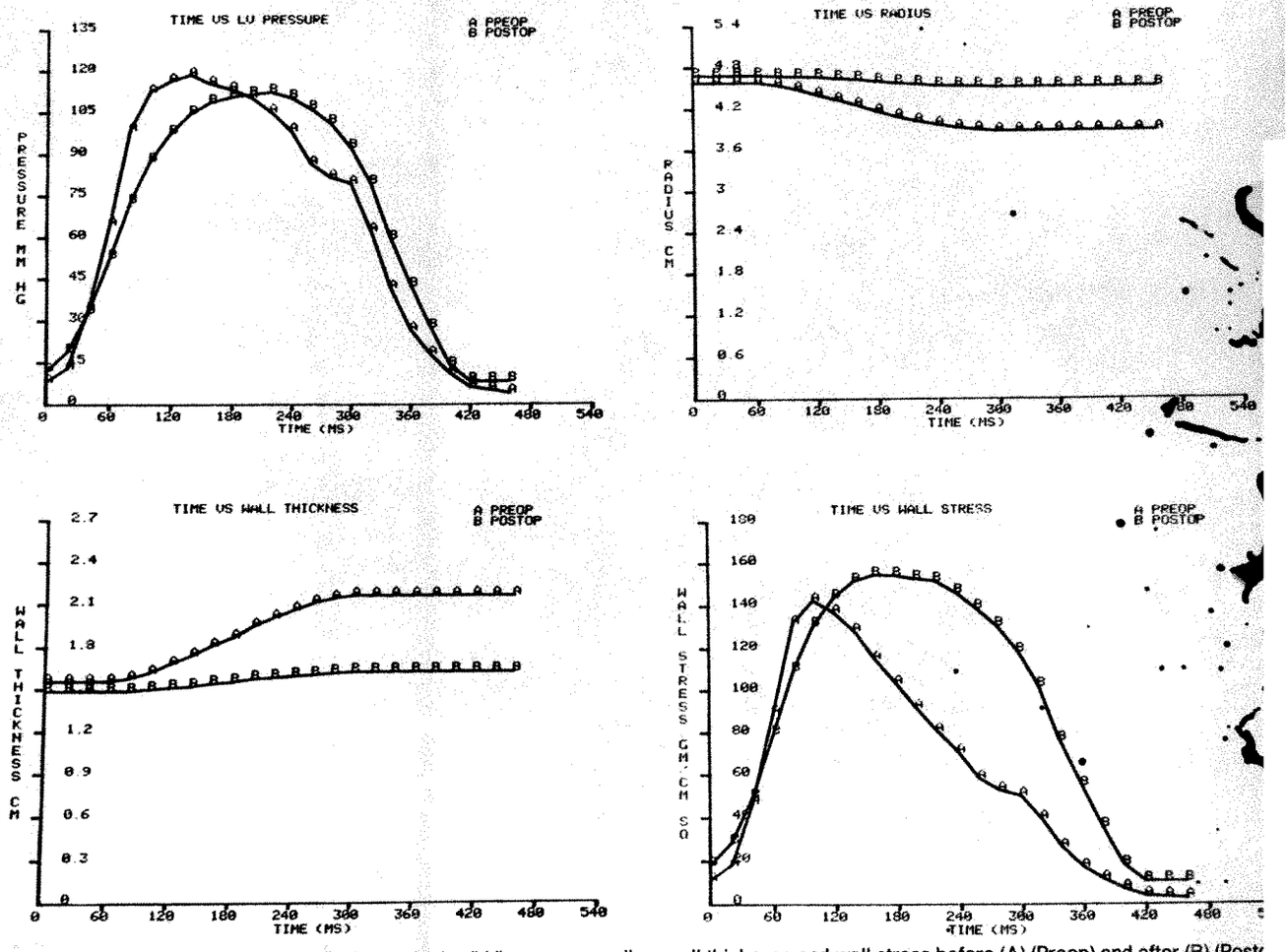

FIGURE 6. Patient 4. Time course of left ventricular (LV) pressure, radius, wall thickness and wall stress before (A) (Preop) and after (B) (Postop) valve replacement for chronic mitral regurgitation.

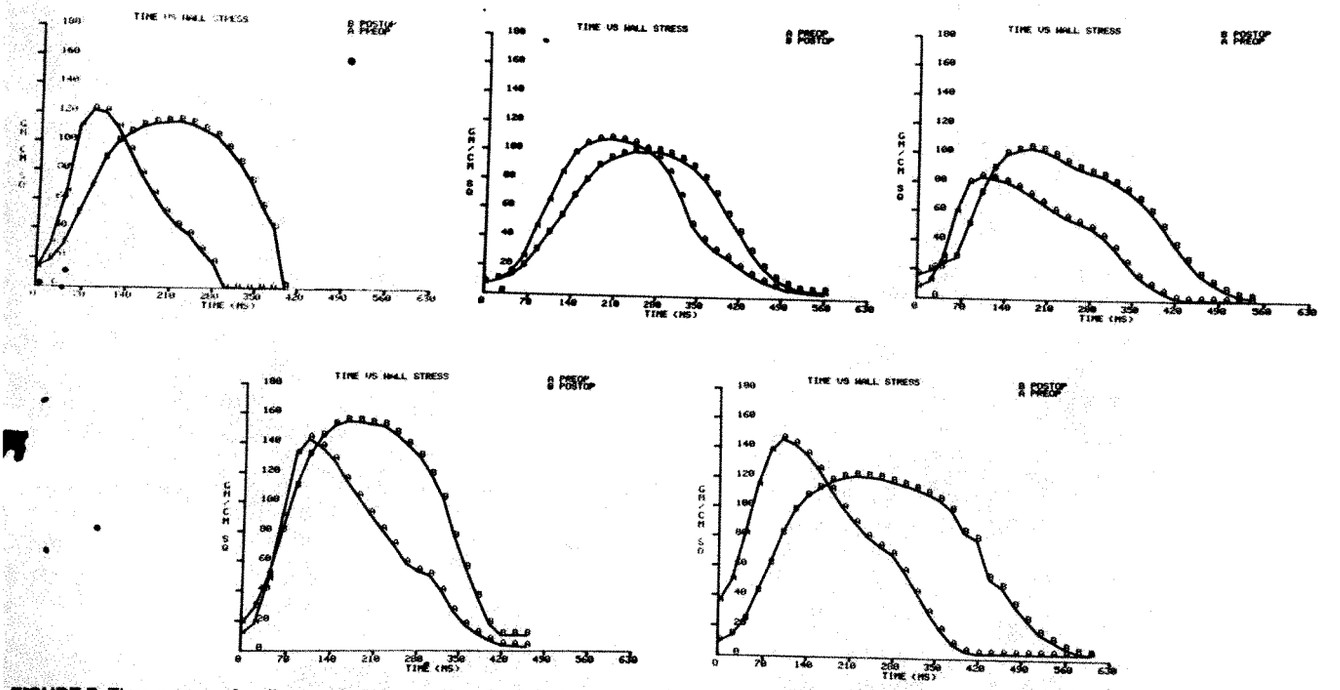

FIGURE 7. Time course of wall stress in five patients with chronic mitral regurgitation preoperatively (A) and postoperatively (B) after valve replacement. A general pattern of an accelerating decrease in systolic wall stress preoperatively and of a sustained increase in systolic wall stress after valve replacement is apparent.

nificantly different. The time course of postoperative wall stress in a representative patient with chronic mitral regurgitation and one with coronary artery disease was also similar (Fig. 8).

Discussion

Our results confirm in human beings the acute occurrence of decreased left ventricular ejection after mitral valve replacement for chronic mitral regurgitation. The data demonstrate statistically significant decreases in both M mode shortening fraction and short axis cross-sectional area reduction during systole. These changes are unique in direction and magnitude to chronic mitral regurgitation, with the notable exception of some patients in our control group who underwent acute correction of aortic insufficiency. Our results are thus consistent with depression of left ventricular function in chronic mitral regurgitation, which is not readily apparent until after valve replacement. Laboratory experiments[4,19,20] suggest that mitral regurgitation is characterized by decreased instantaneous impedance with a low resistance pathway for ejection from the high pressure left ventricle to the low pressure left atrium. The present results confirm this concept in patients and further corroborate that valve replacement eliminates this pathway, increasing impedance throughout systole and leading to the observed decreases in ejection fraction (Fig. 6 and 7). The extent to which preoperative ejection fraction is a useful index of postoperative performance will be dependent on the degree and chronicity of mitral regurgitation and cannot be compared directly with preoperative ejection fraction in most other forms of acquired heart disease.

Short-term postoperative morbidity and mortality are unexpectedly large in chronic mitral regurgitation, with long-term persistence of depressed left ventricular ejection fraction.[6–18] Properties unique to chronic mitral regurgitation appear to promote and maintain hemodynamic function of the left ventricle at the expense of undetected deterioration in muscle function.[4,18–19] Laboratory studies[35–39] associate chronic volume overload with progressive deterioration of ventricular contractility. To assess the degree of depression of left ventricular performance in patients with chronic regurgitation, it is desirable to examine muscle function in comparison with that of control subjects with normal left ventricular geometry, and to assess the impact of structural changes separately.

Structural Changes in Chronic Mitral Regurgitation

Structural changes of eccentric hypertrophy resulting from volume overload: These have been extensively studied and recently reviewed.[40–42] To summarize, acute volume overload results in plastic deformation of the left ventricle, which is initially reversible but ultimately results in a permanently deformed structure.[9,40–47] The result is an increase in ventricular mass,[40,44,48] a rightward shift of the pressure-volume relation (to increased volume at any given filling pressure)[9,40,44,49,50] and an alteration of the relation between sarcomere length and filling volume,

so that relatively normal myocardial sarcomere lengths are observed despite markedly increased volumes.[44] Possible mechanisms for alteration of sarcomere-volume relations include internal "slippage" of longitudinal fiber alignment or alteration of fiber angle relative to the ventricular "equator." Ventricular dilatation results in unfavorable loading conditions, because enlarged radius and diminished wall thickness increase wall stress for any given systolic pressure, according to the modified Laplace relation[30,51] and other analyses of left ventricular wall stress.[19,52,53] This unfavorable change may be partially offset by a reduced requirement for shortening, because a normal stroke volume becomes a small fraction of increased ventricular volume. In addition, increased mass in eccentric hypertrophy can normalize wall stress, if a normal relation of chamber radius to wall thickness (r/h) is preserved.[52,54] In chronic mitral regurgitation peak wall stress appears to be more important than shortening as a determinant of myocardial oxygen consumption, because oxygen consumption does not increase despite increased stroke volume.[4,55] The left ventricle tends toward a spherical or globular shape in chronic mitral regurgitation, rather than the 2:1 ellipsoid observed normally.[9] Because the mechanism of structural rearrangement in chronic mitral regurgitation is not clearly defined, the possibility exists that deposition of noncontractile material in series with contractile elements may contribute to apparent myocardial depression.

Effects on ventricular muscle function: Structural changes are reflected in the present results in parallel increases in left ventricular mass and volume (Table IV) and a tendency (not statistically significant) of the left ventricular pressure-diameter curve to shift to the right (Fig. 3). The volume to mass ratio in our patients with chronic mitral regurgitation averaged 0.87 compared with 0.66 in patients with coronary artery disease, so that a relatively normal relation of r/h was preserved (Table III). A rightward shift of the pressure-diameter curve would result in tolerable filling pressures despite a greatly increased ventricular size. The increased volume observed in chronic mitral regurgitation would otherwise elevate filling pressures beyond compatibility with life. However, increased diastolic compliance, while tending to diminish symptoms, may prolong the course of the disease beyond recovery of normal left ventricular function. The relation of pressure-diameter relations to compliance is a complex issue, because both the shape of the curve and the absolute end-diastolic pressure at any point in time are responsible for the slope of the tangent, dD/dp, which defines compliance. The difficulties of this issue are further demonstrated by animal studies[49,56] of stress versus Lagrangian strain in volume overload, which demonstrate increased left ventricular stiffness even though ventricular volumes are increased at any given filling pressure.

Systolic Mechanics in Chronic Mitral Regurgitation

Comparison of hemodynamic indexes other than ejection fraction immediately after cardiopulmonary bypass reveals little difference between patients

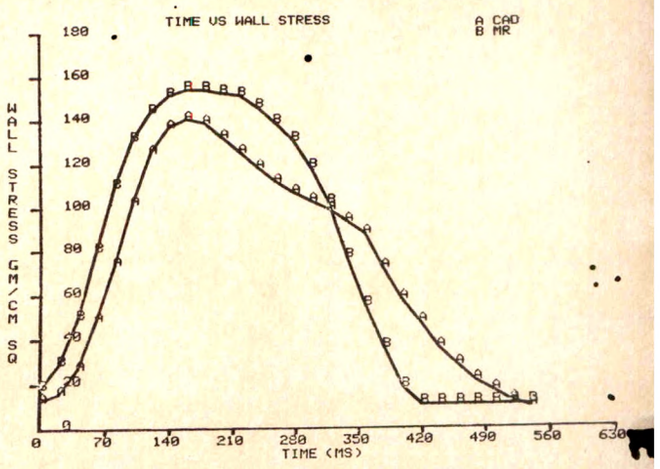

FIGURE 8. Time course of wall stress in a patient after mitral valve replacement for chronic mitral regurgitation (MR) (B) and in a patient after coronary bypass grafting for coronary artery disease (CAD) (A). Little qualitative difference is apparent despite large differences in ventricular dimensions.

undergoing valve replacement for chronic mitral regurgitation and patients undergoing coronary revascularization (Table III). Peak wall stress and the time course of wall stress tended to be normalized postoperatively (Fig. 8), a fortuitous result of relative preservation of chamber radius/wall thickness (r/h) in our patients with eccentric hypertrophy. A tendency toward increased time to peak pressure and flow in chronic mitral regurgitation was not statistically significant. The rate of circumferential fiber shortening (Vcf) was significantly reduced at peak wall stress, as described previously by other investigators.[37] This reflects the fact that the relatively normal stroke volume in postoperative chronic mitral regurgitation is a small fraction of an enlarged end-diastolic volume (that is, ejection fraction is low). Additional differences in functional reserve might be defined by exploration of a wider range of filling pressures, but the large volume of data processing required precludes this at present. Because all patients in our study survived and only one required acute administration of inotropic agents, the mechanics observed may not be representative of the worst seen in patients with chronic mitral regurgitation.

The peak wall stress measurements reported here are low compared with the values of 265 to 560 g/cm^2 preoperatively and 280 g/cm^2 reported postoperatively by other investigators.[37,52,57,58] This is attributable to depressant effects of general anesthesia, the postischemic state immediately after cardiopulmonary bypass, and decreased left ventricular volume during surgery. The acute 39 percent increase in integrated left ventricular wall stress noted after elimination of mitral regurgitation (Table II) may be compared with an average 18 percent increase previously reported in dogs.[19]

The time course of wall stress postoperatively in both patients with chronic mitral regurgitation and

those with coronary disease was strikingly similar; it is strikingly dissimilar from the pattern of chronic mitral regurgitation preoperatively. The latter is thus identified as markedly anomalous in the spectrum of mechanics of human heart disease. This pattern of low impedence that artificially preserves ejection fraction, combined with increased left ventricular compliance that diminishes symptoms of pulmonary venous hypertension, apparently prolongs the time course of the illness to an extreme of left ventricular dysfunction.

Clinical Significance

Present criteria for determining the time of surgical intervention may be inadequate for optimal postoperative results in patients with chronic mitral regurgitation. Several attempts to define new criteria based on heart size or on velocity of circumferential shortening (Vcf) as measured in the catheterization laboratory have yet to be generally accepted. At present, a lower threshold of suspicion is needed to bring patients with chronic mitral regurgitation to earlier clinical attention. Further studies of left ventricular mechanics may help to define new standards for the timing of surgical intervention. Improvements in surgery, including better methods of myocardial preservation, improved valve prostheses and decreased overall morbidity and mortality would also strongly favor early valve replacement. Postoperative treatment of low output states in chronic mitral regurgitation should be directed at afterload reduction in addition to inotropic support, provided filling pressure is adequate. The use of vasopressor agents should generally be avoided.

The observed deterioration of left ventricular ejection fraction after correction of mitral regurgitation does not necessarily imply reduced cardiac output (forward output may actually increase) or clinical deterioration (most patients are symptomatically improved). However, results of surgery will be optimized if excessive unasked deterioration of left ventricular performance can be anticipated and avoided. The unusually high mortality and morbidity rates of surgery for mitral regurgitation suggest that general management of this condition can be improved. Although the depression of left ventricular function observed may reflect ischemia and other events at operation, these factors apply equally to the control patients examined. Furthermore, chronic depression of ejection fraction after correction of mitral regurgitation is well documented.[8,17,18]

Sources of Error

Intraoperative measurement of ventricular volume: The most difficult and important requirement for this study is accurate determination of ventricular volume intraoperatively. Measurement of instantaneous stroke volume is the least difficult, because flow velocity tracings are calibrated by simultaneous thermodilution stroke volume. The determination of end-diastolic volumes by nomogram must be considered less accurate, although the correlation coefficient (0.82) for the relation is satisfactory for our studies. Possible errors are further limited by calculating data for beats with left ventricular end-diastolic pressure close to the values obtained at angiography. However, it is important to point out that intraoperative measurements are obtained with the chest and pericardium open. Both of these changes may influence left ventricular compliance. Our experience suggests that these influences are small, but it is our custom to add 7 mm Hg to the left ventricular end-diastolic pressure observed at angiography to estimate the effects of negative intrapleural pressure and calculate true transmural filling pressure.

Measurement of regurgitant fraction: The greatest potential source of inaccuracy is in the quantitation and timing of that portion of left ventricular volume regurgitated into the left atrium. We have calculated this value from left ventricular end-systolic diameter and our nomogram relating diameter to volume. Calculations have been checked where possible with short axis cross-sectional area changes measured with two dimensional ultrasound and by correlation with regurgitant fraction and ejection fraction measured at preoperative angiography (Table I). The recognized lack of change in shape during systole in the relatively globular left ventricle of chronic mitral regurgitation suggests that the diameter-volume relation is less likely to change during systole with this condition. Whereas observations of decreased ejection fraction with M mode echocardiography alone could reflect paradoxical septal motion, confirmation of the observation with two dimensional echocardiography confirms the presence of global dysfunction of the left ventricle postoperatively.

Conclusions

Intraoperative studies of pressure, flow and echocardiographic dimensions in chronic mitral regurgitation indicate the following:

1. Left ventricular compliance may be increased in chronic mitral regurgitation, as suggested by a tendency toward rightward displacement of the end-diastolic pressure-diameter curve and increased value of the exponential constant.

2. Left ventricular ejection fraction is markedly decreased after mitral valve replacement when measured with either M mode or two dimensional echocardiography. This change is statistically significant when compared with findings in control groups consisting of patients with other common forms of surgical heart disease.

3. The decrease in left ventricular ejection fraction after valve replacement results from acutely increased afterload and elimination of a low impedance pathway to the left atrium.

4. Left ventricular systolic performance in patients with chronic mitral regurgitation is not lower postoperatively than that in patients after revascularization for coronary artery disease when indexes other than ejection fraction and velocity of circumferential shortening are analyzed.

5. Increased left ventricular mass and volume in chronic mitral regurgitation tend to normalize left ventricular wall stress during systole. Nevertheless,

ejection fraction is reduced after valve replacement. This indicates that factors other than peak force generation and pressure work cause decreased ejection fraction postoperatively. These factors may include chronic structural rearrangements in the left ventricular wall and other unrecognized variables.

6. These results emphasize the unreliability of preoperative ejection fraction as an index of cardiac reserve in chronic mitral regurgitation and suggest the need for improved methods of evaluating patients with this condition as candidates for surgery. Conventional analysis of ejection fraction preoperatively will lead to underestimation of the degree of left ventricular dysfunction.

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Right Ventricular Performance in Mitral Stenosis

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Until recently, the dynamic geometry and pump function of the pressure-overloaded right ventricle in patients with mitral stenosis and pulmonary hypertension had not been well defined. With use of a recently developed method for calculating right ventricular volume in human beings, seven normal subjects and eight patients with mitral stenosis and pulmonary hypertension had right ventricular performance assessed from computer-analyzed biplane right ventriculograms. Patients with mitral stenosis had elevated values for systolic right ventricular pressure (mean ± standard error of the mean 25 ± 2 for normal subjects, 57 ± 6 mm Hg for patients with mitral stenosis), but normal values for right ventricular end-diastolic volume index (normal 95 ± 11, patients 81 ± 9 ml/m^2) and ejection fraction (normal 0.49 ± 0.02, patients 0.58 ± 0.04). Comparison of right ventricular function using group performance curves of stroke work versus end-diastolic volume revealed the slope of the mitral stenosis line to be significantly greater than the normal line. A plot of right ventricular stroke volume versus end-diastolic volume, which removes pressure from the performance index, revealed that the two groups have similar performance. Left ventricular function measured by ejection fraction was reduced in mitral stenosis. These data suggest that the right ventricle performs normally in patients with mitral stenosis with moderate pulmonary hypertension and maintains normal size and ejection fraction.

The clinical and hemodynamic effects of long-standing untreated mitral stenosis are well known.[1–4] It is also known that chronic pressure overload on the right ventricle because of mitral stenosis can result ultimately in right ventricular failure.[2–5] Although there has been extensive description of the clinical and hemodynamic status of the right ventricle subjected to chronic pressure overload, little is known about the contractile state of this chamber when the pressure overload is secondary to mitral stenosis.

Previous studies[6] evaluating the contractile state of the pressure overloaded right ventricle utilized pressure-dependent measurements to analyze right ventricular performance. However, such measurements may be misleading in the state of chronic pressure overload. Because the increased systolic load imposed on the right ventricle necessitates an augmented contractile response to maintain flow against higher resistance, the performance of the right ventricle, as assessed from pressure measurements, may appear normal or elevated.

In this study, we analyzed right ventricular performance in the state of chronic pressure overload using measurements of right ventricular volume as well as pressure. From this analysis, we have found that the contractile performance of the right ventricle in mitral stenosis remains normal with moderate pressure overload when there is no clinical evidence of right ventricular failure.

Methods

Study patients: The study is based on 14 patients who underwent diagnostic right and left heart catheterization including biplane right and left ventriculography. Seven patients had mitral stenosis as the only significant valve lesion. Patients with significant occlusive coronary artery disease were excluded. No

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of the seven patients with mitral stenosis had clinical evidence of right ventricular failure (edema, hepatomegaly, ascites, right ventricular third sound). Two of the seven had minimal tricuspid regurgitation on right ventriculography. Three had atrial fibrillation, and four had normal sinus rhythm. The average heart rate was 91 ± 8.6 beats/min (the range was 60 to 120). Seven patients with normal right and left heart pressures and normal findings on right and left ventriculography and coronary arteriography served as control subjects.

Catheterization procedure: All patients underwent diagnostic cardiac catheterization using the right brachial technique.[7] Left heart catheterization was performed with a 7F National Institutes of Health catheter. Biplane 60 frame/s left ventriculography was performed using Renografin® -76 injected at 12 to 16 cc/s for 3 seconds, with the patient in the 60° left anterior oblique and 30° right anterior oblique positions. After coronary arteriography and repair of the brachial arteriotomy, right ventriculograms were exposed at 60 frames/s with the patient in the 60° left and 30° right anterior oblique positions using Renografin-76 injected at 12 to 16 cc/s for 3 seconds. Pressure measurements in both ventricles were obtained with Statham p23dB fluid-filled transducers connected to the ventricular catheters. Right ventricular pressure measurements were made with a 7F fluid-filled pigtail catheter connected to Statham p23dB pressure transducers with a zero reference at the level of the mid chest.

Right ventricular volume analysis: One and one-half cardiac cycles beginning at the peak of the electrocardiographic R wave were analyzed. Ventriculographic outlines from each frame of the biplane films were digitized with a digital plotting table connected to a computer.[8] The two ventricular outlines were traced with a magnetic cursor and the geometric data were stored on digital tape. Volume analysis for the right ventricle is based on an area-length method that we[9] previously described. To calculate stroke work, a right ventricular pressure wave form was digitized and superimposed on the already stored ventriculographic image data. Calculation of stroke work was done using the formula: $SW = \Sigma\, p\,dv$, where p is instantaneous pressure in a given 1/60 second interval and dv is the change in volume over the same interval. The value for dv is calculated by determining the first derivative of a second order curve drawn through the volume curve in the region of analysis. Further details of this calculation are given in a previous study.[8] The integral of the work versus time curve from end-diastole to end-systole provides the stroke work. End-diastole and end-systole were determined from the volume versus time curve. End-diastolic, end-systolic and stroke volumes were also obtained from the curve of right ventricular volume versus time constructed from the frame by frame analysis.

Left ventricular ejection fraction was calculated from the end-diastolic and end-systolic frames in the left and right anterior oblique views. The left ventricular volumes were determined using the formula of Dodge et al.[10]

Statistical analysis: For comparisons between normal subjects and patients with mitral stenosis, nonpaired *t* tests were used. Linear regression was used to derive the slopes of the ventricular function curves. Data are expressed as mean values ± standard error of the mean.

Results

Left heart pressures and volumes (Table I): There was no significant difference between the left ventricular end-diastolic volume index of the patients with mitral stenosis and the control group, whereas the left ventricular end-systolic volume index was slightly higher in the patient group. There was no significant difference between the left ventricular stroke volume index of the patients and control subjects. The left ventricular ejection fraction was lower in the patients than in the control subjects ($p < 0.05$). There was no significant difference between the peak systolic pressure or end-diastolic pressure of the left ventricles of the two groups.

Right heart pressures and volumes (Table II): The mean pulmonary arterial wedge pressure for the patients with mitral stenosis was 23.3 ± 2.3 mm Hg and the mean mitral valve gradient at rest averaged 11.9 ± 1.6 mm Hg. The average mitral valve area calculated from the Gorlin formula[11] was 1.0 ± 0.17 cm^2. Right ventricular ejection fraction in the patients was somewhat higher than that in the control subjects ($p < 0.10$), but there was no difference between the right ventricular end-diastolic volume index and right ventricular stroke volume index of the two groups. The end-systolic volume index was somewhat lower in the patients than for the control group, but this difference was not significant. Average right ventricular systolic pressure was

TABLE I

Left Ventricular Characteristics in Seven Normal Subjects and Seven Patients With Mitral Stenosis*

	Normal Subjects	Patients With Mitral Stenosis
EDVI (ml/m^2)	79.4 ± 7.4	88.6 ± 10.0
ESVI (ml/m^2)	25.3 ± 3.2	37.5 ± 6.0
SVI (ml/m^2)	54.1 ± 5.4	51.5 ± 6.6
EF	0.68 ± 0.03	0.53 ± 0.03†
EDP (mm Hg)	9.3 ± 1.3	10.1 ± 2.1
PSP (mm Hg)	123.6 ± 9.6	130.0 ± 6.0

* Data are expressed as mean values ± standard error of the mean.
† $p < 0.05$ compared with normal value.
EDP = end-diastolic pressure; EDVI = end-diastolic volume index; EF = ejection fraction; ESVI = end-systolic volume index; PSP = peak systolic pressure; SVI = stroke volume index.

TABLE II

Right Ventricular Characteristics in Seven Normal Subjects and Seven Patients With Mitral Stenosis*

	Normal Subjects	Patients With Mitral Stenosis
EDVI (ml/m^2)	94.9 ± 10.8	80.7 ± 9.2
ESVI (ml/m^2)	48.5 ± 6.4	33.9 ± 4.8
SVI (ml/m^2)	45.7 ± 4.9	46.9 ± 6.1
EF	0.49 ± 0.02	0.58 ± 0.04
EDP (mm Hg)	2.4 ± 0.77	5.8 ± 1.7
PSP (mm Hg)	25.1 ± 1.60	56.6 ± 6.1†
dP/dt (mm Hg/s)	304.2 ± 53.3	593.8 ± 84.7†
SWI (joules/m^2)	0.111 ± .014	0.253 ± .045†

* Data are expressed as mean values ± standard error of the mean.
† $p < 0.05$ compared with normal value.
dP/dt = first derivative of left ventricular pressure; SWI = stroke work index; other abbreviations as in Table I.

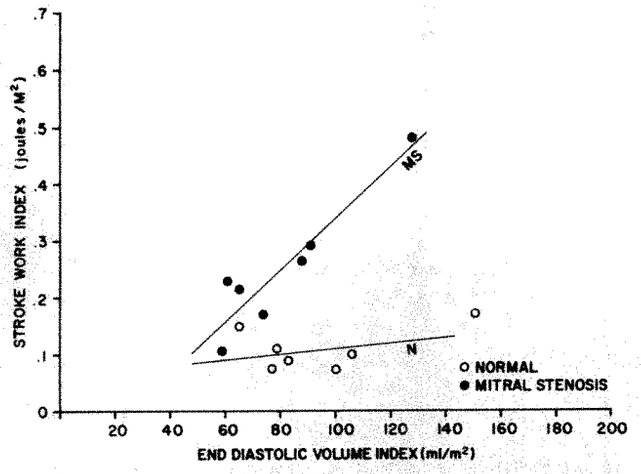

FIGURE 1. Comparison of right ventricular function in seven normal subjects (N) and seven patients with mitral stenosis using group performance curves of stroke work versus end-diastolic volume. The slope of the mitral stenosis (MS) line is significantly greater than the normal (N) slope.

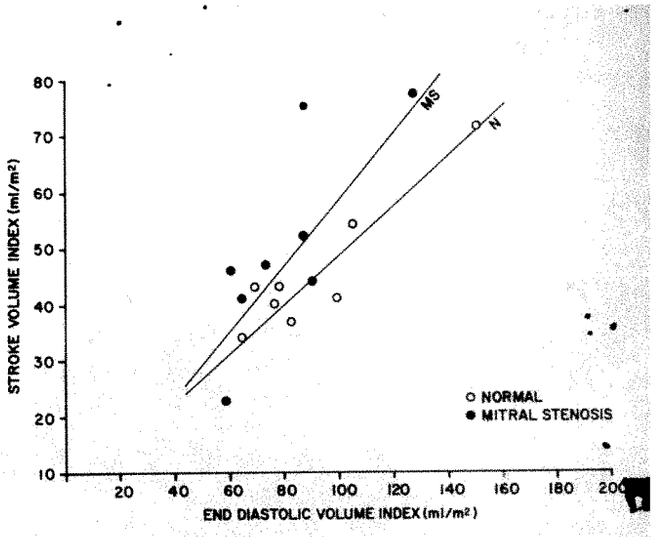

FIGURE 2. Comparison of right ventricular function in normal subjects (N) and patients with mitral stenosis (MS) using group performance curves of stroke volume versus end-diastolic volume. When pressure is removed from the performance measurement, the two groups have similar contractile performance.

significantly higher in the patients. The mean right ventricular end-diastolic pressure in the patients was slightly higher than that in the control group, although this value remained within the normal range and the difference was not significantly different.

Right and left ventricular performance: *Right ventricle:* A plot of stroke work index versus end-diastolic volume index for patients with mitral stenosis and for the normal control subjects (Fig. 1) revealed a significantly higher slope in the patients (normal = 5.54 ± 5.13, patients = 45.15 ± 8.00; $p < 0.005$). The slope of stroke volume index versus end-diastolic volume index for the patients and control subjects (Fig. 2) showed no significant difference between groups (normal = 0.430 ± 0.63, patients = 0.586 ± 0.143). Right ventricular peak rate of pressure development (dP/dt) was increased (Table II) in the patients.

Left ventricle: A plot of left ventricular stroke volume index versus end-diastolic volume index in the patients with mitral stenosis and the control subjects (Fig. 3) revealed a slightly lower slope in the patient group; however, the difference was not significant (normal = 0.675 ± 0.124, patients = 0.527 ± 0.176).

Discussion

Right ventricular volume and pump performance in chronic pressure overload: Our observations demonstrate that the right ventricle maintains normal volume and contractile performance in the presence of moderate pressure overload induced by mitral stenosis. Although it is known that a prolonged severe systolic overload can result in right ventricular failure with edema, ascites, hepatic congestion and venous distension, our study did not include patients with fulminant right ventricular failure. Whereas right ventricular performance studies are rare, studies of left ventricular contractile function in chronic pressure overload have demonstrated that left ventricular contractile performance remains normal until overt clinical failure occurs.[12,13] Data from our laboratory[13] also indicate that left ventricular volume remains normal despite chronic pressure overload to the left ventricle unless overt failure is present. Thus, the ventricles appear to respond similarly when subjected to chronic pressure overload. The data of Sasayama et al.[14] in dogs indicated that the right ventricle functions normally in states of m pressure overload and, in cats, Williams and Potter found normal right ventricular function after 24 wee of moderate pressure overload even though function w initially depressed. Our data in the present stu

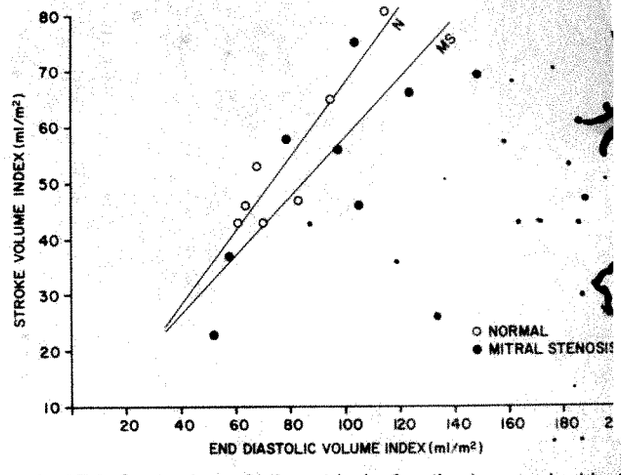

FIGURE 3. Comparison of left ventricular function in normal subjects (N) and patients with mitral stenosis (MS) using group performance curves of stroke volume versus end-diastolic volume. Although the slope of the mitral stenosis line is lower than the normal slope, the difference did not reach statistical significance.

demonstrate that right ventricular volume and right ventricular pump performance are normal with moderate pressure overload and in the absence of overt clinical right ventricular failure. Normal right ventricular pump function with moderate systolic pressure elevation may progress to decreased function when the pressure load becomes severe. Other clinical[12,13] and animal[16,17] studies of chronic pressure overload have shown that ventricular performance is a function of the severity of the overload.

Assessment of right ventricular performance: The assessment of intact right ventricular performance in the presence of chronic pressure overload is difficult. Pressure-related indexes such as peak right ventricular pressure, dP/dt, stroke work and stroke power will always suggest augmented performance because of the elevated systolic pressure. The right ventricle must generate excess pressure to maintain forward blood flow. This increased pressure generation is usually made possible by increased myocardial mass (hypertrophy), and measurement of pressure does not allow assessment of the contribution of increased muscle mass to performance.

A recent study by Stein et al.[6] using pressure-based performance characteristics demonstrated normal contractile function of the right ventricle in patients with pulmonary hypertension including nine with clinical right ventricular failure. They used plots of right ventricular dP/dt versus end-diastolic pressure to determine ventricular performance. Nine of their patients had overt clinical failure but showed normal function on the basis of pressure measurements.

We[18] have previously used plots of stroke volume versus end-diastolic volume to assess intact left ventricular performance in animal studies where systolic pressure was elevated. These volume curves applied to the present right ventricular data (Fig. 2) show that right ventricular function is normal in mitral stenosis without overt right ventricular failure.

Although normal right ventricular pump performance was demonstrated in our patients, we cannot state with certainty that muscle performance of the right ventricle is normal. A disparity between pump and muscle performance may occur, for example, when normal pump performance is maintained by hypertrophy of poorly performing muscle units. It was impossible in the present study to assess the degree of right ventricular hypertrophy.

Left ventricular performance in mitral stenosis: Although this study was primarily concerned with right ventricular performance, we noted (Table I) that the left ventricular ejection fraction of the patients with mitral stenosis was lower than that of normal subjects. Abnormal left ventricular function in patients with mitral stenosis[19–21] has previously been reported, but its cause is not clear. It is possible that a pressure overload to the right ventricle in some way affects the left ventricle through changes in right ventricular shape that may be reflected into the left ventricle through the shared interventricular septum.[22] The left ventricle of these patients may also have been affected by inflammatory changes at the time of active rheumatic disease[23,24] or by fibrosis of the chordae tendineae and papillary muscles.[25] Finally, it is possible that the pump function of the left ventricle may be affected by a decrease in inflow to the left ventricle because of valve obstruction.[26]

In summary, we have demonstrated that the right ventricle functions normally when subjected to chronic pressure overload due to mitral stenosis. This normal function is probably maintained by hypertrophy when the pressure overload is not extreme. In addition, left ventricular performance appears to be diminished in mitral stenosis, and the cause of this reduced left ventricular function is not clear.

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Right Ventricular Function in Adult Atrial Septal Defect

Preoperative and Postoperative Assessment and Clinical Implications

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Right ventricular function was assessed with gated cardiac blood pool scanning in 20 adult patients with an atrial septal defect. All patients had scans both before and 6 or more months after surgical repair of the defect. Clinical findings, pre- and postoperative course and cardiac catheterization data were correlated with scan findings. In all 20 patients, the right ventricle was dilated preoperatively. In nine patients (aged 18 to 42 years, mean 25), right ventricular wall motion was normal preoperatively. All nine were asymptomatic and had normal sinus rhythm. Their pulmonary to systemic flow ratio ranged between 2:1 and 5:1, pulmonary arterial systolic pressure between 18 and 30 mm Hg and right ventricular end-diastolic pressure between 0 and 8 mm Hg. After repair of the atrial septal defect, all nine remained asymptomatic, right ventricular size decreased dramatically and wall motion was normal.

In the remaining 11 patients (aged 36 to 63 years, mean 52), there was moderate to severe preoperative right ventricular hypokinesia. All had preoperative symptoms (functional class II and III, New York Heart Association); six had atrial fibrillation and five had normal sinus rhythm; seven had clinical heart failure. Pulmonary to systemic flow ratio ranged between 1.7:1 and 5.0:1, pulmonary arterial pressure between 26 and 70 mm Hg and right ventricular end-diastolic pressure between 4 and 16 mm Hg. Symptoms were lessened and right ventricular size and function improved postoperatively in these 11 patients. Unlike those with normal preoperative right ventricular wall motion, however, only 1 of the 11 had normal postoperative right ventricular function and became asymptomatic.

Most patients with isolated atrial septal defect undergo elective surgical repair during childhood or early adult life before either symptoms or complications develop. In such patients postoperative complications are uncommon.[1–3] In contrast, older adults with an uncorrected atrial septal defect frequently have symptoms and pre- and postoperative complications, particularly atrial arrhythmias and right heart failure.[4–9] Although these symptoms and complications are generally attributed to chronic right heart volume overload, to our knowledge right ventricular systolic function has not previously been systematically studied in these patients.

Gated cardiac blood pool imaging has been extensively used to assess right ventricular function in a wide range of cardiac lesions,[10–14] and is well suited to the noninvasive assessment of right ventricular size and function in patients with atrial septal defect. In this study, we assessed right ventricular function using gated cardiac blood pool imaging in 20 patients before and after repair of an atrial septal defect, and correlated these findings with clinical and catheterization data and with the postoperative course.

Methods

Study patients: Twenty patients (aged 18 to 63 years) with isolated secundum atrial septal defect documented by cardiac catheterization or surgery, or both,

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were studied. A preoperative gated cardiac blood pool scan was performed at the time of cardiac catheterization in all patients, and a postoperative follow-up scan was performed 6 months after surgical correction. Pre- and postoperative clinical course, cardiac medications, physical examination, cardiac rhythm and cardiac catheterization findings were reviewed and correlated with data obtained from the gated cardiac scan. Symptoms and functional class were categorized according to standard New York Heart Association criteria.[15] Right heart failure was defined by abnormal elevation of jugular venous pressures, hepatomegaly, ascites and edema.

Imaging techniques: Radionuclide scanning was performed after intravenous administration of 20 millicuries of either technetium-99m labeled human serum albumin or in vivo labeled red blood cells.[16] Gated scans were recorded at only end-systole and end-diastole in the initial 13 patients; the last 7 patients had multigated scans. Studies were recorded with an all purpose collimator using a 20 percent window centered at the 140 KeV photopeak of technetium-99m. The data were recorded using a dedicated nuclear medicine computer PDP-9 system for the initial 12 patients, and an Ohio Nuclear VIP-450 in the last 8. In the latter eight patients, the initial passage of tracer through the right side of the heart was recorded in the right anterior oblique projection in a multiple gated acquisition sequence during the first 5 to 10 beats after the tracer injection.

Assessment of right ventricular function: Although there have been some published reports proposing criteria for assessing right ventricular size and contraction by gated cardiac scan,[12,17] quantitative criteria have not been universally agreed on. Thus, in this study, we relied primarily on the subjective assessment of the experienced nuclear medicine physician. Scans were interpreted independently by us on three separate occasions without knowledge of the patients' clinical or catheterization findings. There was no significant interobserver variability in interpretation. There were no discernible differences in our results using either method of cardiac imaging, that is, end-systolic and end-diastolic differences in the initial 13 patients versus estimation of these points from the multigated scans performed in the last 7 patients.

Right ventricular size was subjectively graded as normal (Fig. 1B) or dilated (Fig. 1A, 3A, 3B). In addition, subjective observations were supplemented by more quantitative evaluation by comparing the right ventricular and left ventricular areas determined with planimetry at end-diastole in the left anterior oblique projection. Previous work[12] indicates that the normal right ventricular size only slightly exceeds left ventricular size, with the ratio of normal right ventricular to left ventricular size being 1.11 ± 0.06 (mean ± 1 standard deviation). In patients with an isolated atrial septal defect, left ventricular size is typically normal; therefore this ratio was used as a measure of right ventricular size.

Right ventricular contraction was assessed subjectively and graded as normal (Fig. 1 and 2) or hypocontractile (Fig. 3 and 4). A more quantitative assessment of right ventricular contraction was also made by calculating the right ventricular ejection fraction in eight patients who had gated first pass

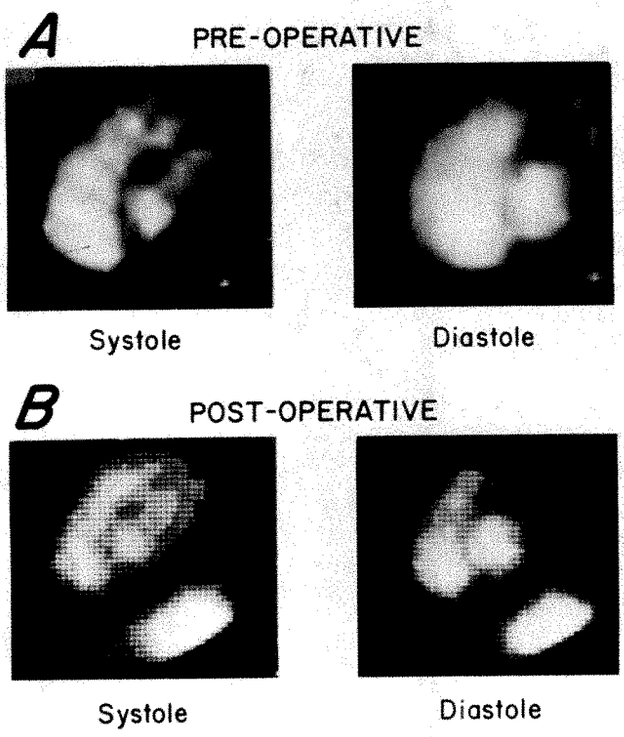

FIGURE 1. Pre- (**A**) and postoperative (**B**) equilibrium gated cardiac blood pool scan in the left anterior oblique projection in a 25 year old woman with an atrial septal defect. Preoperatively, the right ventricle is dilated (right ventricle/left ventricle ratio = 2.15/1) but has normal wall motion (ejection fraction = 64 percent). The postoperative scan performed 6 months after surgical repair reveals decreased right ventricle size (right ventricle/left ventricle ratio = 1.36/1), and normal right ventricular contraction (ejection fraction = 65 percent).

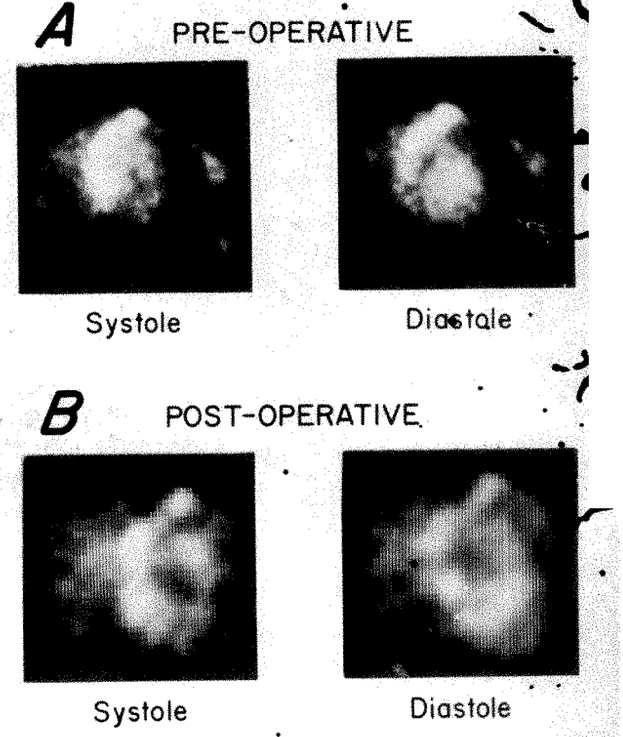

FIGURE 2. Pre- (**A**) and postoperative (**B**) gated first pass flow scans in the right anterior oblique projection in a 36 year old woman with an atrial septal defect, illustrating normal pre- and postoperative right ventricular contraction with an ejection fraction of 58 and 64 percent, respectively.

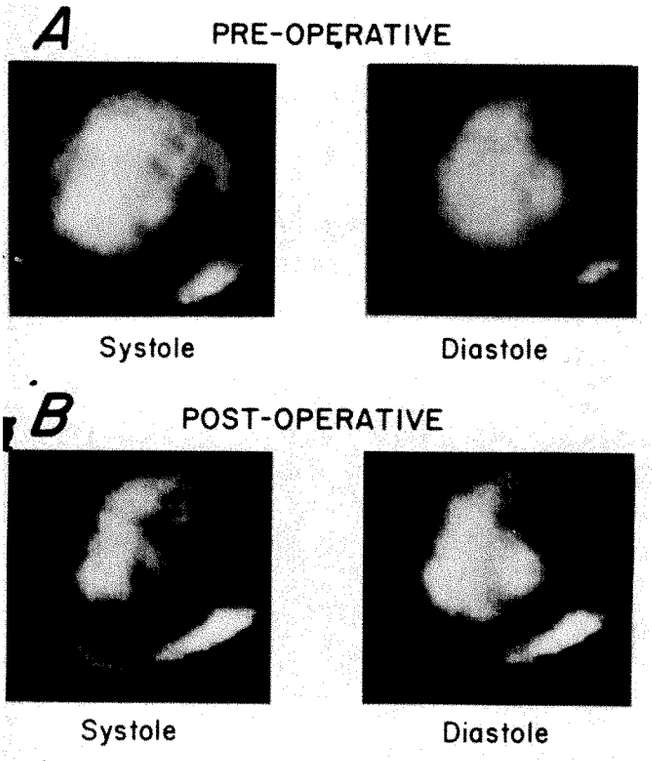

FIGURE 3. Pre- (**A**) and postoperative (**B**) gated cardiac blood pool scans in the left anterior oblique projection in a 58 year old woman with an atrial septal defect, moderate pulmonary hypertension and heart failure. Preoperatively, the right ventricle is markedly dilated (right ventricle/left ventricle = 3.5:1) and severely hypokinetic (ejection fraction = 36 percent). Postoperatively (after 6 months), there is a decrease in right ventricular size (right ventricle/left ventricle ratio = 3.0:1) but persisting right ventricular hypokinesia (ejection fraction = 50 percent).

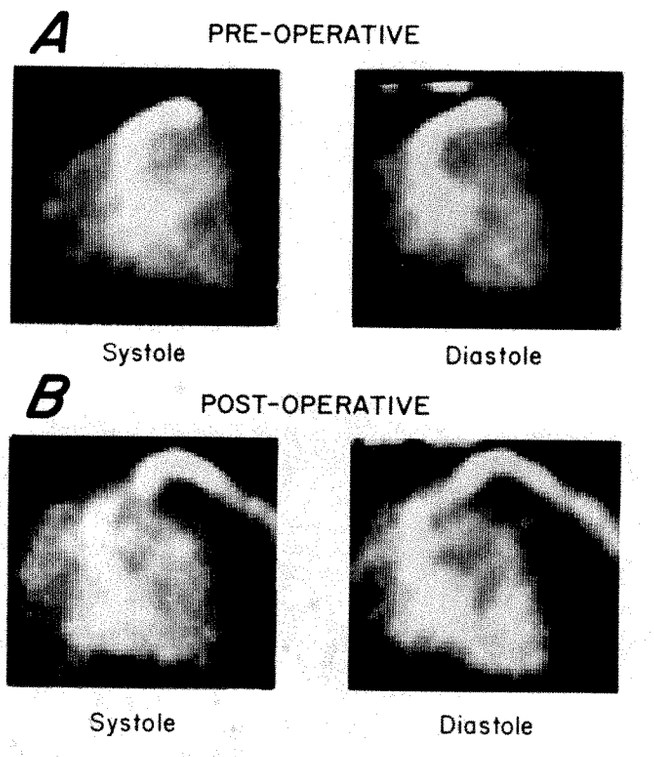

FIGURE 4. Pre- (**A**) and postoperative (**B**) gated first pass flow scans in the right anterior oblique projection in a 52 year old woman with an atrial septal defect illustrating decreased pre- and postoperative right ventricular contraction with an ejection fraction of of 46 and 45 percent, respectively.

ans. In these patients, right ventricular ejection fraction was calculated using a previously reported method[17] in which ejection fraction was determined as the difference between end-systolic and end-diastolic counts in the right ventricular region in the right anterior oblique first pass study. With this technique, normal right ventricular ejection fraction in our laboratory is 60 ± 7.0. In addition, right ventricular ejection fraction was determined by the difference between end-systolic and end-diastolic area determined by planimetry in the left anterior oblique projection. This value did not differ significantly from the ejection fraction determined using the counts method.

Results

Subjective preoperative right ventricular dilation of varying magnitude was present in all patients (Fig. 1A and 3A). The ratio of planimetered right ventricular to left ventricular area in these patients ranged between 1.89 and 3.50:1. Assessment of preoperative right ventricular wall motion separated patients into two clinically and hemodynamically distinct subgroups.

Patients with normal right ventricular wall motion: Nine patients (aged 18 to 42 years, mean 25) had normal right ventricular wall motion, inspite of varying degrees of dilation (Fig. 1A and 2A). The ratio of planimetered preoperative right ventricular to left ventricular areas ranged between 1.84 and 2.15:1 (mean 2.0:1) and the calculated preoperative ejection fraction ranged between 58 and 70 percent (mean 64). All patients were asymptomatic and none had heart failure or arrhythmias. Nine required cardiac medication. Pulmonary-to-systemic flow ratio ranged between 2 and 5:1, pulmonary artery systolic pressure between 18 and 30 mm Hg, (mean 23 mm Hg), pulmonary artery resistance was less than 2 units · m^2 in all patients, and right ventricular end-diastolic pressure was between 0 and 8 mm Hg (mean 3). All patients had uncomplicated repair of the atrial septal defect, none had postoperative symptoms or complications, and the postoperative scans revealed marked decrease in right ventricular size (Fig. 1B) and normal right ventricular wall motion (Fig. 1B, 2B). The ratio of planimetered postoperative right ventricular to left ventricular areas was between 1.36 and 1.43:1 (mean 1.40) and postoperative right ventricular ejection fraction was between 64 and 66 percent, (mean 65).

Patients with right ventricular hypokinesia: Eleven patients (aged 36 to 63, mean 52) had diffuse preoperative right ventricular hypokinesia (Fig. 3A, 4A). Planimetered preoperative right ventricular to left

ventricular area ratio in these patients was between 2.81 and 3.50:1 (mean 3.10:1). Preoperative ejection fraction was between 31 and 47 percent (mean 34 percent). All of these patients had preoperative exertional fatigue and dyspnea (functional class II or III); five were in atrial fibrillation and six in normal sinus rhythm. Seven patients had clinical findings of heart failure consisting of elevated jugular venous pulse and hepatomegaly, and two patients had ascites, edema, and tricuspid incompetence. Nine patients required digitalis preparations and five also required diuretics. Pulmonary to systemic flow ratio ranged between 1.7 and 5.0:1; pulmonary artery systolic pressures between 26 and 70 mm Hg (mean 43); pulmonary artery resistance between 2 and 5.5 units · m^2 (mean 3.8); and right ventricular end-diastolic pressure between 4 and 16 mg Hg (mean 11).

Symptoms improved in all patients after surgical repair and they were either in functional class I or II but only one patient (age 36 years) became asymptomatic. Atrial fibrillation persisted postoperatively in the five patients who had preoperative atrial fibrillation and the remaining patients remained in normal sinus rhythm. Digitalis preparations were continued in nine patients and diuretics in three. The postoperative scan showed subjective decrease in right ventricular size in all patients but still significant dilation, and all had persistent right ventricular hypokinesis (Fig. 3B, 4B). The ratio of postoperative right ventricular to left ventricular planimetered area was between 1.5 and 3.0:1 (mean 2.20:1). Postoperative right ventricular ejection fraction was between 44 and 51 percent (mean 47), which was a significant increase compared to preoperative right ventricular ejection fraction ($p < 0.05$).

Discussion

Right ventricular function following repair of atrial septal defect: Although it is presumed that chronic right ventricular volume overload causes impairment of right ventricular ejection in the adult with atrial septal defect, and that this explains their symptoms and complications, there have been few systematic studies of right ventricular function in these patients. Preoperative right ventricular wall motion in our patients varied from normal to reduced. Preoperative right ventricular wall motion divided patients into two groups in terms of pre- and postoperative symptoms and complications, and normal versus abnormal postoperative right ventricular function. Right ventricular wall motion was normal in the asymptomatic younger patients even though the right ventricle was enlarged. These patients remained asymptomatic after surgery, right ventricular size decreased dramatically, and right ventricular wall motion remained normal. In contrast, patients with decreased preoperative right ventricular wall motion were older and had pre- and postoperative symptoms or complications, or both. In these patients, postoperatively right ventricular dilation also decreased and right ventricular wall motion and symptoms improved; however, right ventricular function did not become normal. Although symptoms improved postoperatively, these patients did not become asymptomatic.

Prior studies have evaluated postoperative right ventricular size using M mode echocardiography,[18] and findings in both the young[19] and older[20] patient with atrial septal defect closely mirror our findings using gated cardiac imaging. However, as demonstrated in the present study, right ventricular function appears to be an important predictor of pre- and postoperative clinical status in these patients and this has not previously been systematically assessed using a noninvasive radionuclide approach. Selective right ventricular angiography is suitable for evaluating right ventricular contraction, but in the older patient with heart failure and elevated pulmonary artery pressure it is not without risk.[21] Two dimensional echocardiography may also be helpful in assessing right ventricular size and wall motion[22]; however, to our knowledge it has not yet been systematically applied to these patients.

Clinical implications: Our observations strongly support the present widespread clinical practice of early prophylactic closure of atrial septal defect. Furthermore, in spite of only partial postoperative improvement in symptoms and right ventricular size and function in patients with abnormal preoperative right ventricular wall motion, our findings also argue strongly for surgical repair in these patients.

The correlation between right ventricular wall motion and postoperative improvement in right ventricular size and function in patients with atrial septal defect observed in our study is analogous to the correlation between preoperative left ventricular wall motion and postoperative improvement of left ventricular size and function in patients with aortic insufficiency.[23,24] In the latter, decreased preoperative left ventricular wall motion also indicates that postoperative left ventricular function may not normalize.

Of note was the presence of right ventricular hypokinesis in four patients who had clinical right ventricular failure with elevated right ventricular end-diastolic pressure, but who had normal pulmonary artery pressure (less than 30 mm Hg), pulmonary arteriolar resistance between 2 and 4 units · m^2, and normal coronary arteries. These patients illustrate the not widely appreciated fact that severe pulmonary hypertension is not the only cause of right ventricular failure in atrial septal defect.[1,8,25]

In summary, this study illustrates the close correlation between right ventricular function and clinical course in both pre- and postoperative patients with atrial septal defect. Nuclear imaging is helpful in assessing the older symptomatic adult. In these patients, the demonstration of severe preoperative right ventricular hypocontractility indicates that, although postoperative right ventricular size and function improve, neither becomes normal.

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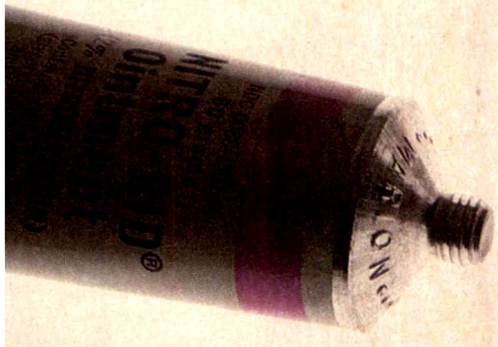
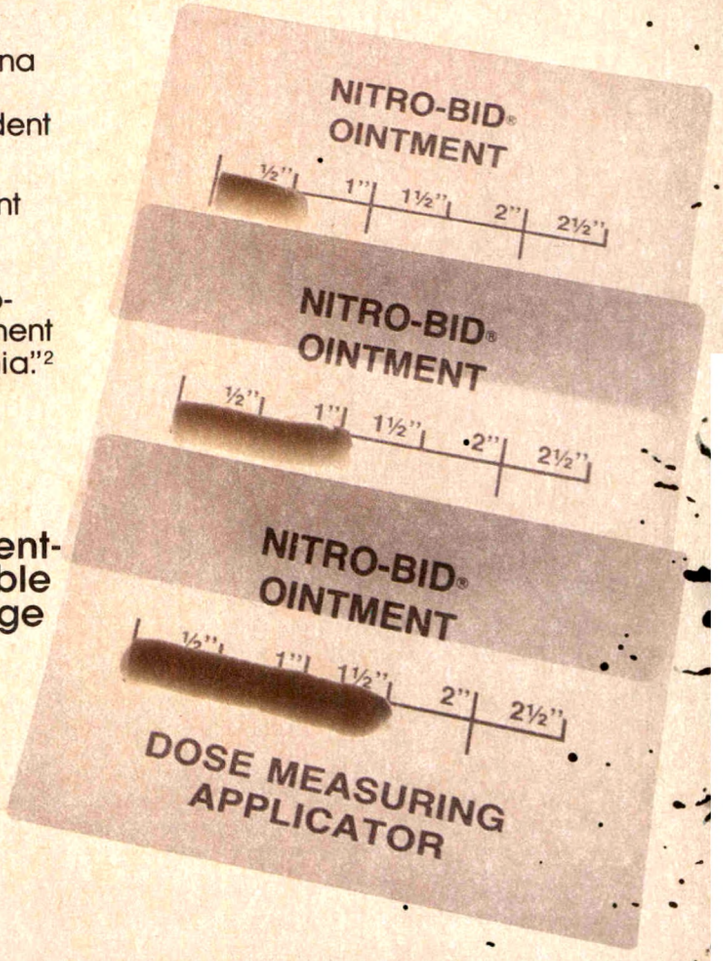


Patient-titratable dosage



Brief Summary:

Description: Nitroglycerin 2% (glyceryl trinitrate) and lactose in a special absorptive lanolin and white petrolatum base.

Action: Nitroglycerin is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effects.

Indications: For the prevention and treatment of angina pectoris due to coronary artery disease.

Contraindications: In patients known to be intolerant of the organic nitrate drugs.

Warnings: In acute myocardial infarction or congestive heart failure, nitroglycerin ointment should be used under careful clinical and/or hemodynamic monitoring.

Precautions: Symptoms of hypotension, particularly when suddenly arising from the recumbent position, are signs of overdosage. When they occur, the dosage should be reduced.

Adverse Reactions: Transient headaches are the most common side effect, especially at higher dosages. Headaches should be treated with mild analgesics, and nitroglycerin ointment continued. Only with untreatable headaches should the dosage be reduced. Although uncommon, hypotension, an increase in heart rate, faintness, flushing, dizziness, and nausea may occur. These all are attributable to the pharmacologic effects of nitroglycerin on the cardiovascular system, but are symptoms of overdosage. When they occur and persist, the dosage should be reduced.

Dosage: Usual dose is 2 inches (50mm), as squeezed from the tube, every eight hours. Some patients may need 4 to 5 inches (100 to 125 mm) and/or application every four hours. Optimal dosage should be based upon clinical response, side effects, and effects of therapy upon blood pressure. Consult full product disclosure before prescribing.

References:

1. Davidov M, Mroczek W: The effect of nitroglycerin ointment on exercise capacity in patients with angina pectoris. Presented at American College of Pharmacology meeting, Washington DC, April 1977.

2. Awan NA, Miller RR, Maxwell KS, et al: Cardiocirculatory and antianginal actions of nitroglycerin ointment: Evaluation by cardiac catheterization, forearm plethysmography and treadmill stress testing. Chest 73:14-18 (Jan) 1978.

7/80

Another patient benefit product from

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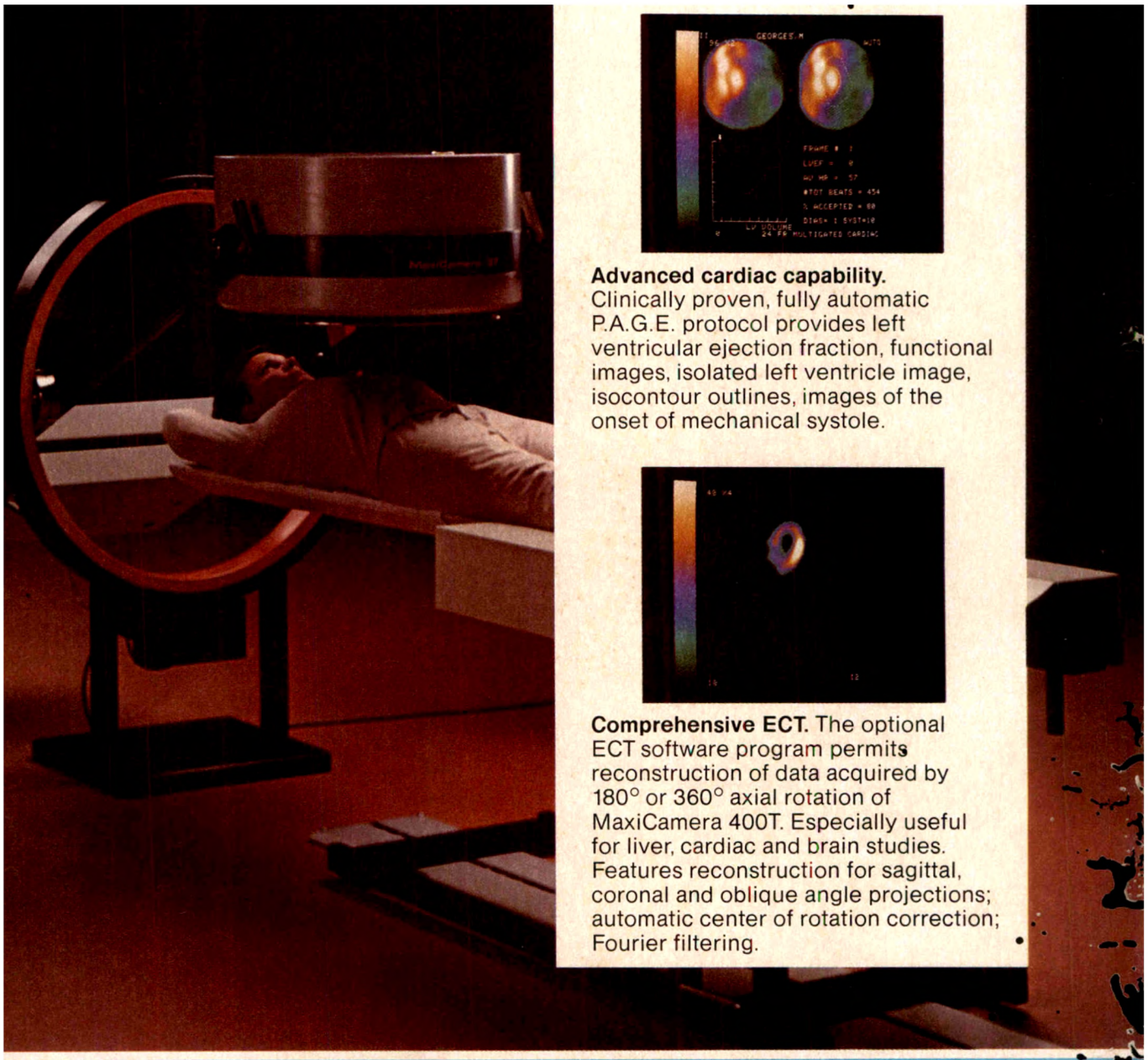

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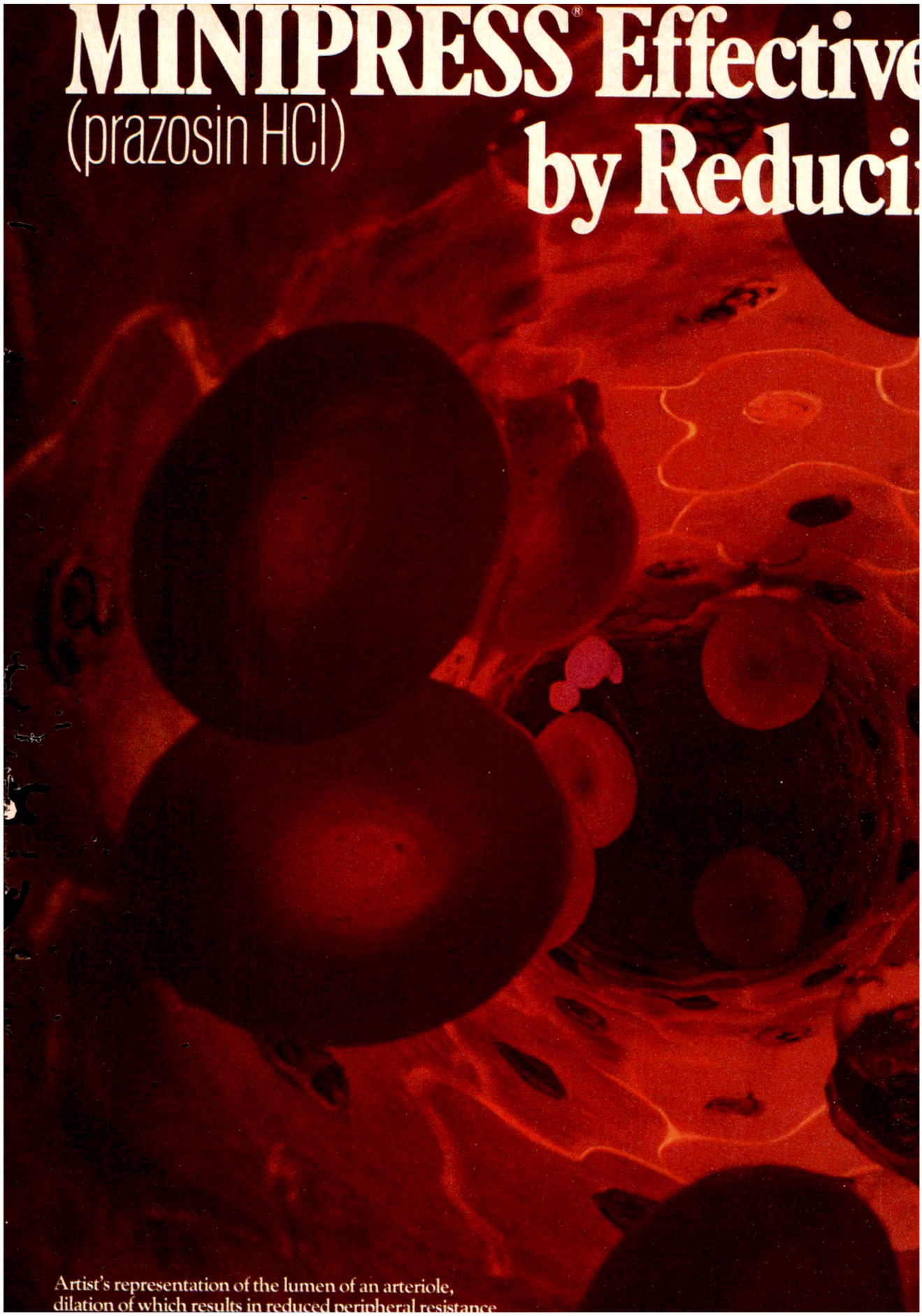
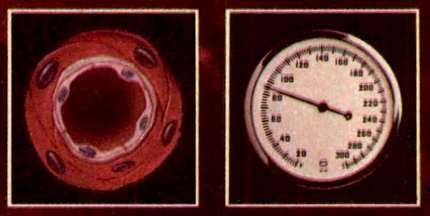
MINIPRESS® Effective
(prazosin HCl)
by Reduci



Artist's representation of the lumen of an arteriole, dilation of which results in reduced peripheral resistance

Controls Hypertension Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
- MINIPRESS Reduces Total Peripheral Resistance
- MINIPRESS Does Not Reduce Cardiac Index

...and Maintains These Effects Over the Long Term

Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen[1]

Rest Exercise

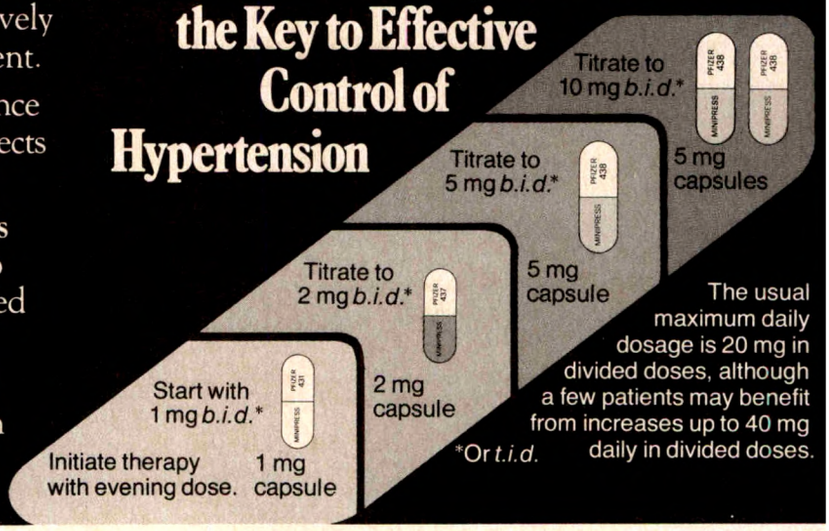
MINIPRESS®

(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

MINIPRESS
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

- **Effectively lowers elevated blood pressure by reducing peripheral resistance.**
- **Maintains cardiac output** which allows patients to maintain an active life style.
- **Maintains renal blood flow and glomerular filtration rate** so it can be used effectively even in patients with renal impairment.
- **Not a CNS agent** so patients experience few of the troublesome CNS side effects that impair their quality of life.
- **Cardiovascular response to exercise is preserved** so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- **A small percentage of patients** have experienced orthostatic hypotension and syncope.

B.I.D. Dosage Titration... the Key to Effective Control of Hypertension



BRIEF SUMMARY

MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.

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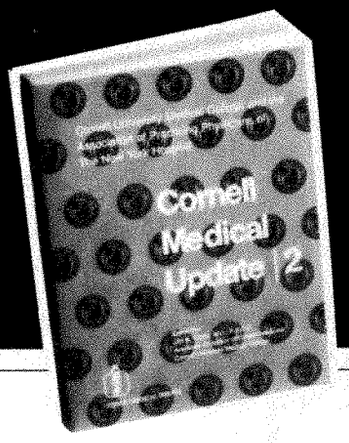

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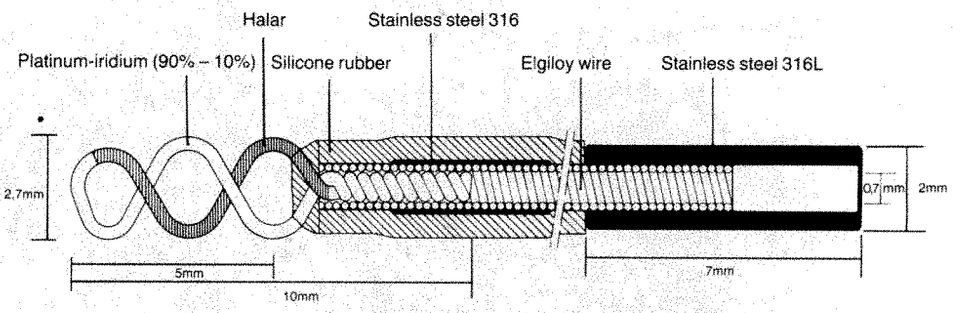
The Helifix electrode. What it can do in the ventricle, it can do in the atrium.

In the relatively short time since Vitatron first introduced Helifix* for ventricular pacing, its wide acceptance has told us something.



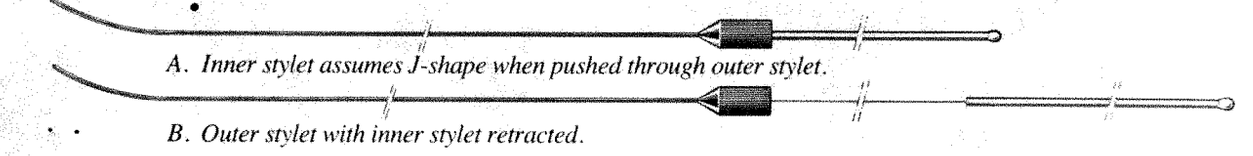
If, we reasoned, Helifix had proven so effective for ventricular pacing — 2 or 3 turns let you twist it securely into the trabeculae — it was entirely logical that it should work equally as well for atrial pacing.

And it does.

Essentially, what we've done is develop a new *double* stylet. An inner, pre-bent stylet assumes a rigid, J-shape when it's pushed through a second, outer stylet.

The result is that you can easily pull the lead upward, implanting the helical coil securely into the atrial appendage. Atraumatically. And without risk of puncturing the delicate atrial wall.

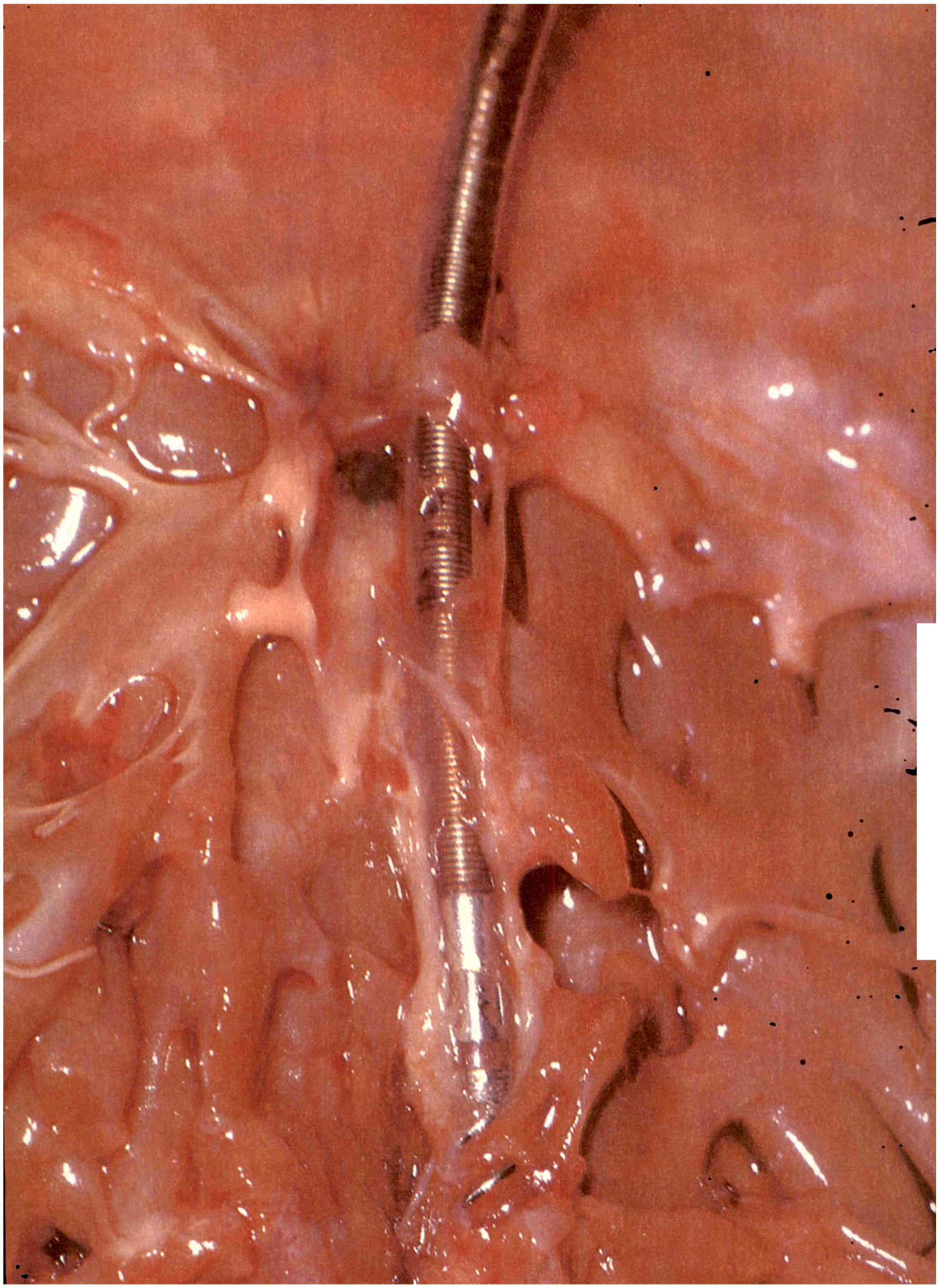
For a secure, positive solution to atrial fixation, we urge you to consider Helifix. For our latest data, including clinical evaluations, or to arrange a private screening of our new Helifix film, write: Vitatron Medical, B.V., P.O. Box 76, Dieren, The Netherlands. In the United States, call (617) 964-1980.



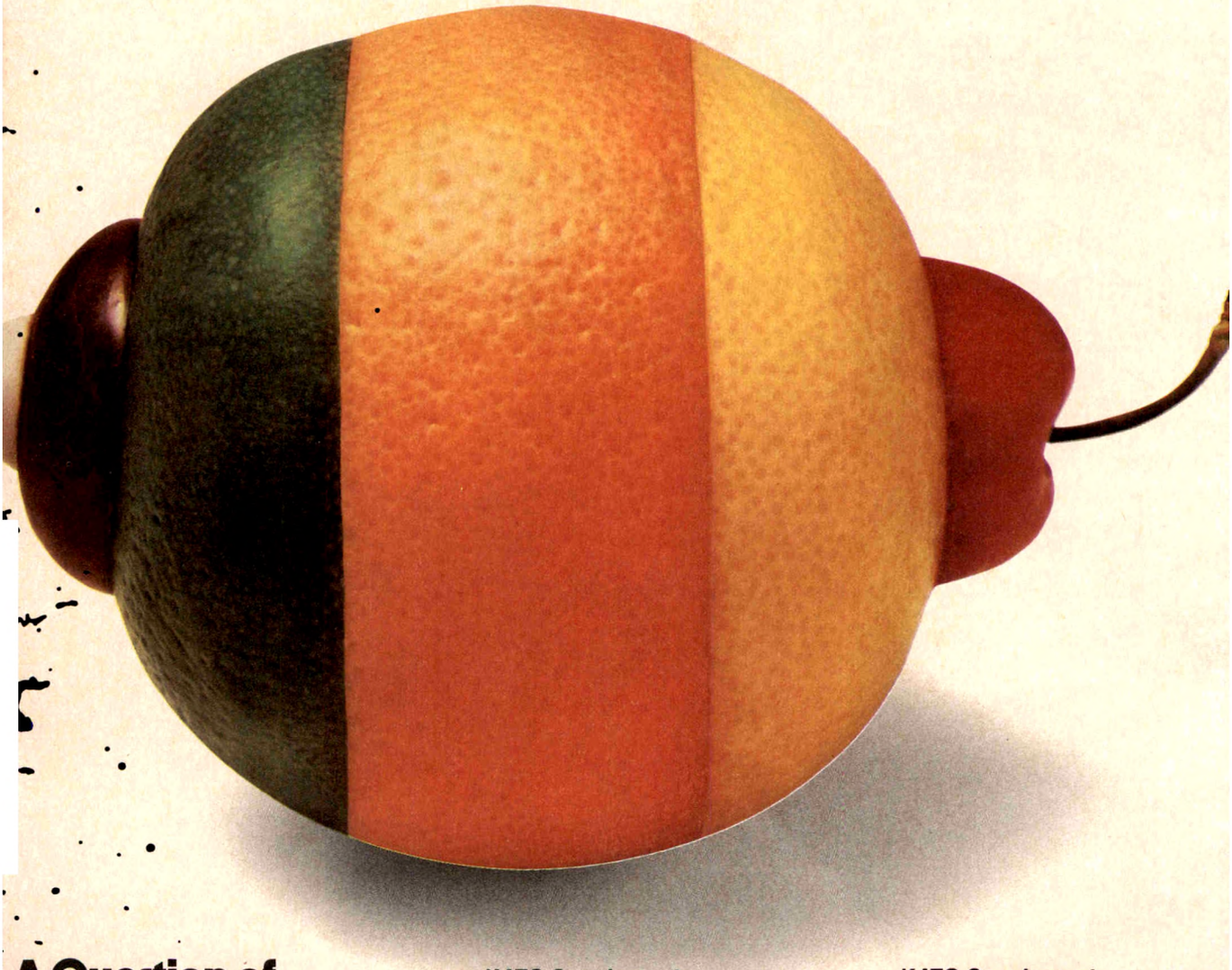
A. Inner stylet assumes J-shape when pushed through outer stylet.

B. Outer stylet with inner stylet retracted.

Vitatron Medical



Fruitless?



A Question of Compliance.

Patients on potassium supplements *won't* comply if they tire of the sweet fruity taste used to mask the "bitter pill" of potassium in their medication.
That's when a prescription for fruitless taste of KATO potassium supplement can be fruitful.

KATO Supplement. The compatible taste of tomato.

In KATO supplement, the naturally tangy taste of tomato *complements* the naturally salty taste of potassium chloride. Patients like the combination, and will stay with it day after day. Tomato-flavored KATO supplement is a natural — at breakfast and dinner.

KATO Supplement. The preferred salt in the preferred form.

Each single-dose packet of KATO supplement contains 20 mEq of potassium chloride — the preferred salt — and less than 5 mg sodium chloride. Because it contains the chloride salt, KATO supplement can be used where hypochloremic alkalosis is also a problem. KATO supplement mixes easily in water or tomato juice, and just two packets daily provide a full therapeutic dose.

Fruitful.

KATO Supplement.
It's fruitless for fruitful compliance.

- tangy, tomato taste well accepted for long-term compliance
- B.I.D. regimen encourages compliance
- liquid form minimizes potential for gastrointestinal irritation
- corrects both hypokalemia and hypochloremic alkalosis
- convenient, easy-to-carry single-dose packets

KATO®
(potassium chloride for oral solution) 20 mEq (1.5 g KCl)

SYNTEX

SYNTEX PUERTO RICO, INC.
HUMACAO, PUERTO RICO 00661

Please see prescribing information on following page.

KATO®
(potassium chloride for oral solution)
20 mEq (1.5 g KCl)

Prescribing Information

DESCRIPTION:
Spray-dried tomato powder containing 20 mEq potassium (equivalent to 1.5 g KCl) per 6 grams powder (one dose) with natural and synthetic flavors, spices and colors. Benzoic acid and potassium benzoate added as preservatives. When reconstituted as directed, makes a pleasantly flavored, low sodium tomato juice drink. Each daily dose (2 packets) contains approximately 0.5 mEq sodium.

INDICATIONS:
The prevention or correction of potassium deficit, particularly when accompanied by hypochloremic alkalosis in conjunction with thiazide diuretic therapy, in digitalis intoxication, or as the result of long-term corticosteroid therapy, low dietary intake of potassium, or excessive vomiting or diarrhea.

CONTRAINDICATIONS:
Potassium is contraindicated in severe renal impairment involving oliguria, anuria or azotemia; in untreated Addison's disease, familial periodic paralysis, acute dehydration, heat cramps, hyperkalemia from any cause. Potassium chloride should not be employed in patients receiving potassium-sparing agents such as aldosterone antagonists and triamterene.

PRECAUTIONS:
KATO is a concentrate and should be taken only after reconstituting with water as directed. This preparation, like other potassium supplements, must be properly diluted to avoid the possibility of gastrointestinal irritation. Do not use in patients with low urinary output or renal decompensation. Administer with caution; it is impossible to assess accurately the daily dose required. Excessive dosage may result in potassium intoxication. Frequent checks of the clinical status of the patient, ECG and/or plasma potassium level should be made. High plasma concentrations of potassium ion may cause death through cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease.

ADVERSE REACTIONS:
Vomiting, diarrhea, nausea, and abdominal discomfort may occur. Gross overdosage may produce signs and symptoms of potassium intoxication: mental confusion, listlessness, paresthesia of the extremities, weakness and heaviness of legs, flaccid paralysis, hyperkalemia, ECG abnormalities, fall in blood pressure, cardiac arrhythmias and heart block. The characteristic changes in the ECG are disappearance of the P wave, widening and slurring of QRS complex, changes of the S-T segment, tall peaked T waves, etc.

TOXICITY:
Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours.

TREATMENT OF HYPERKALEMIA:
1. Dextrose solution 10% or 25% containing 10 units of crystalline insulin per 20 g dextrose, given I.V. in a dose of 300cc to 500cc in an hour. 2. Adsorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally or as retention enema. 3. Hemodialysis or peritoneal dialysis. 4. Elimination of potassium-containing foods and medicaments. Warning: Digitalis toxicity can be precipitated by lowering the plasma potassium concentration too rapidly in digitalized patients.

ADMINISTRATION AND DOSAGE:
Mix with water to make a pleasant tomato juice drink. Each 6-gram unit dose packet provides 20 mEq of potassium. Usual adult dose—1 packet of KATO mixed with about 2 ounces of water twice daily—supplies 40 mEq potassium per day. Take with meals or follow with ½ glass of water. Larger doses may be required, but should be administered under close supervision because of the possibility of potassium intoxication.

HOW SUPPLIED:
Cartons of 30 and 120 6-gram unit dose packets, 20 mEq each.

CAUTION:
Federal law prohibits dispensing without a prescription.

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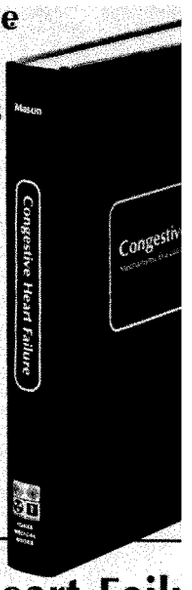

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovasc University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Soci Research.

Member of the American Board of Internal Medicine Cardiovascular

Has authored more than 400 original articles on cardiovascular scier cardiology.

Serves on the editorial boards of The American Journal of Cardiology, Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the Amer Pharmacology and Experimental Therapeutics, the Research Awards the American Therapeutic Society, and the Theodore and Susan Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State D the American College of Cardiology.

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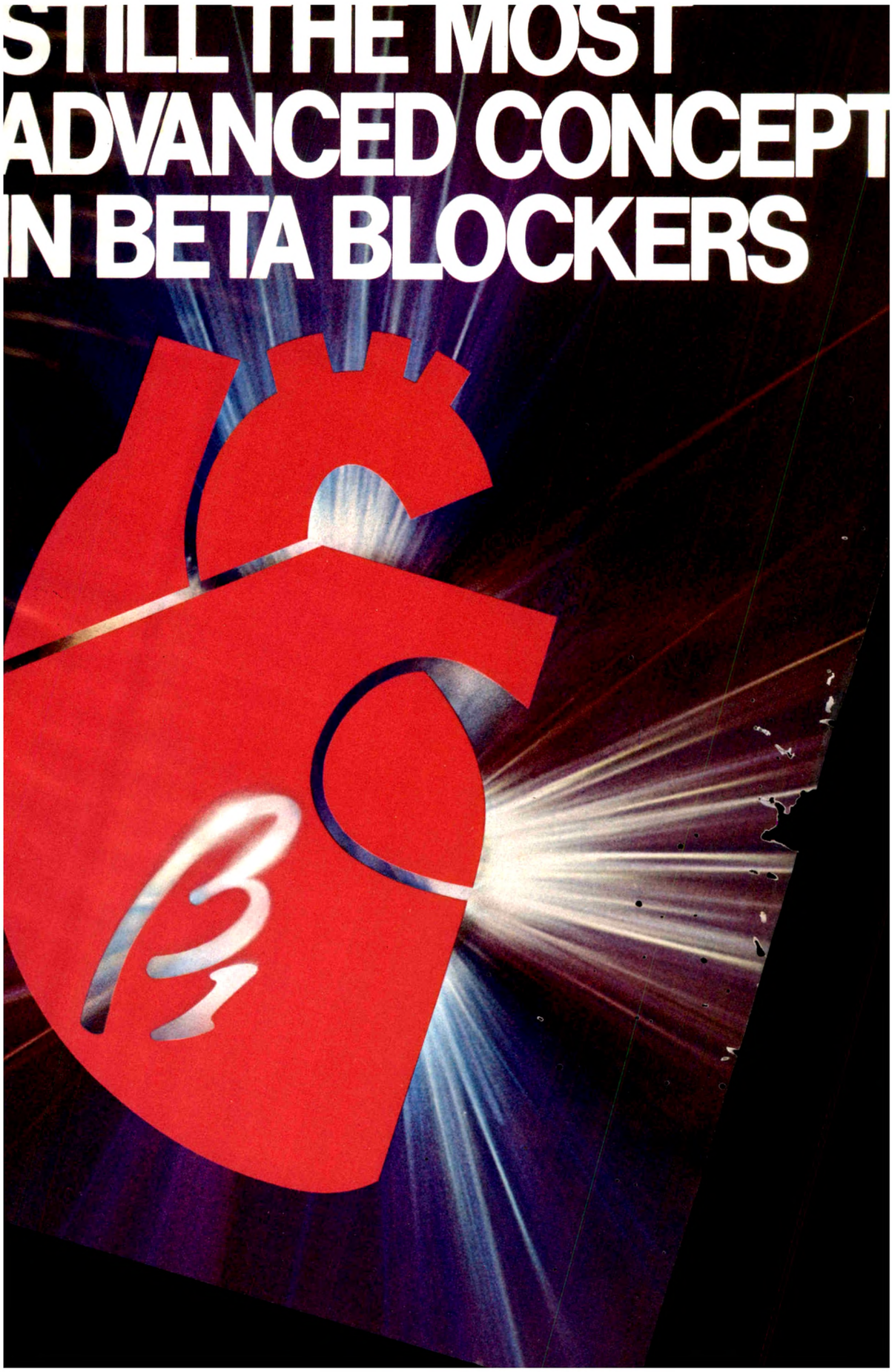
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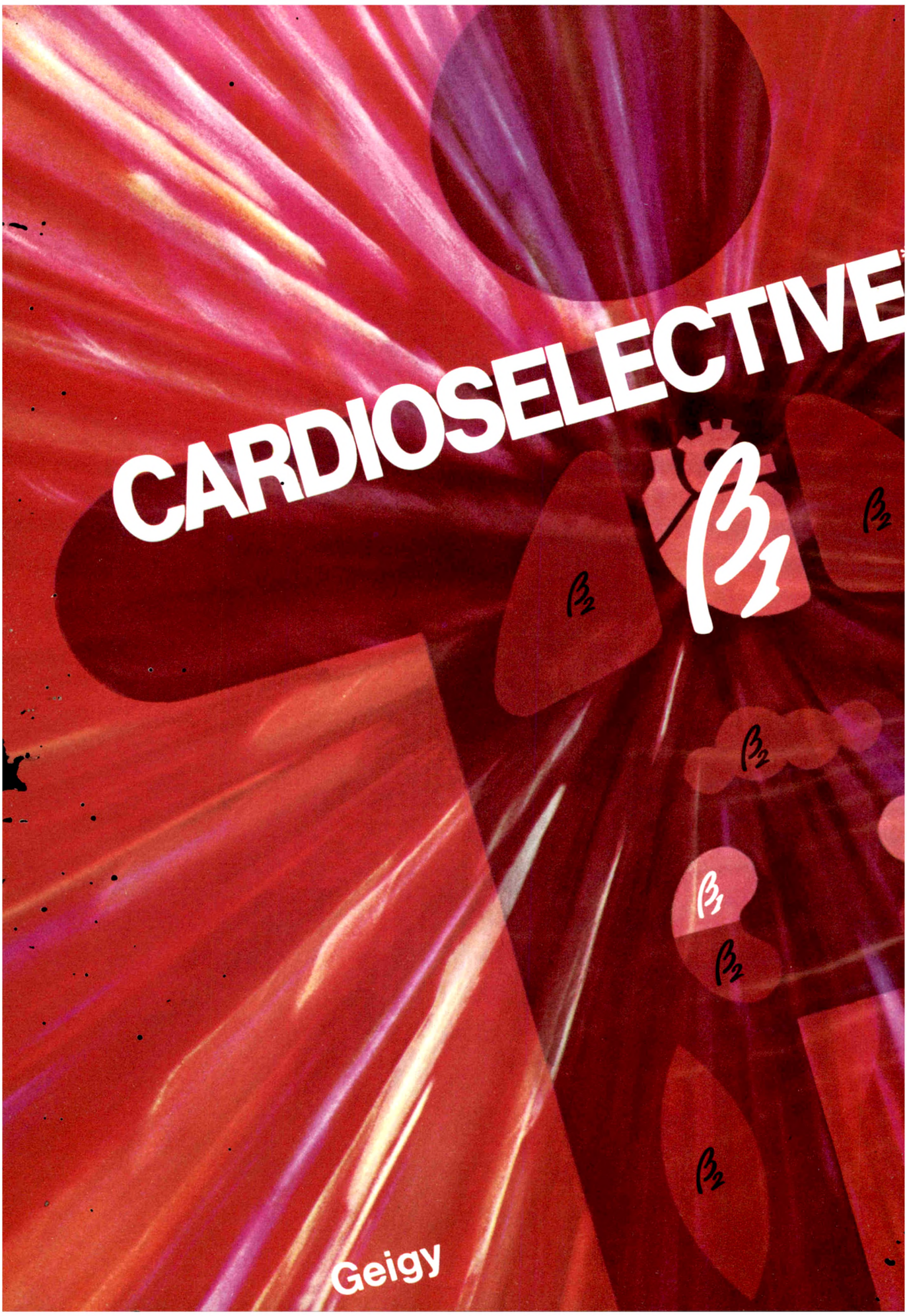
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exerts a relative preference for beta-one receptors.

WORKS WHERE IT SHOULD– NOT WHERE IT SHOULDN'T– IN HYPERTENSION

By concentrating its action on the beta-one receptors involved in blood pressure control and to a large extent—at usual therapeutic dosages—avoiding the unwanted effects of beta-two blockade, Lopressor offers potential benefits not available with the nonselective beta blockers.

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LESS EFFECT ON PERIPHERAL CIRCULATION AFTER EXERCISE[1]
Propranolol, due to beta-two blockade, causes a greater reduction in muscle blood flow than does Lopressor.

REDUCES THE PRESSOR EFFECT OF EPINEPHRINE[2]
Propranolol augments the pressor effect of epinephrine, while Lopressor reduces the pressor effect.

BETTER TOLERABILITY IN PATIENTS WITH ASTHMA[3]
At an antihypertensive dosage (100 mg daily) there was no difference in FEV, and no patients reported any influence on their asthma.

Lopressor should be used with caution in patients with bronchospastic disease. Since beta-one selectivity is not absolute, bronchospastic patients should receive a beta-two-stimulating agent concomitantly. For complete details, see the Warnings section of the prescribing information.

Please see next page for brief summary of prescribing information.

B2

Lopressor®
metoprolol tartrate

An antihypertensive beta-blocking agent

Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities, arterial insufficiency, usually of the Raynaud type, palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 100 or less.

Allergic: Pruritus has occurred in less than 1 of patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

Store at controlled room temperature and protect from moisture.

Dispense in tight, light-resistant container (USP).

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For complete details, including description, clinical pharmacology and overdosage, please see full prescribing information.

References

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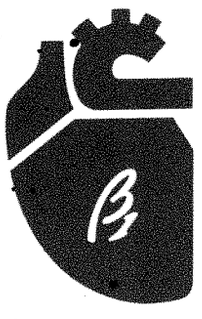

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Acute Effects of Ethanol on Myocardial Blood Flow in The Nonischemic and Ischemic Heart

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To determine the effects of ethanol on myocardial blood flow in the nonischemic and ischemic heart, coronary blood flow was measured with radionuclide-tagged microspheres in the anesthetized dog before and after intravenous administration of 1.7 g/kg body weight of ethanol. In nonischemic dogs, at an average peak blood ethanol level of 225 ± 8 mg/dl (mean ± standard error of the mean), left atrial pressure increased from 5.7 ± 0.6 to 7.7 ± 0.8 mm Hg ($p < 0.01$) and heart rate slowed from 179 ± 8 to 171 ± 8 min^{-1} ($p < 0.001$) but mean aortic pressure and cardiac output were unchanged. Average myocardial blood flow increased from 122 ± 5 to 143 ± 8 ml/min per 100 g ($p < 0.001$). In dogs given ethanol after coronary occlusion, at an average peak blood ethanol level of 201 ± 13 mg/dl, left atrial pressure increased from 6.3 ± 0.6 to 7.4 ± 1.4 mm Hg ($p < 0.05$) but there was no significant change in heart rate, mean aortic pressure or peak positive first derivative of left ventricular pressure (dP/dt). In these dogs, there was a significant change ($F = 6.47$, $p < 0.001$) in the distribution of myocardial blood flow. In the nonischemic zone, blood flow increased from 118 ± 7 to 148 ± 14 ml/min per 100 g ($p < 0.005$), whereas in the ischemic zone it declined from 30 ± 6 to 20 ± 5 ml/min per 100 g ($p < 0.02$). Myocardial tissue demonstrating myocardial perfusion equal to or greater than 80 percent of preligation levels showed a significant increment of blood flow after ethanol; by contrast, myocardial tissue having blood flow levels equal to or less than 60 percent of preligation levels showed a significant decline in blood flow.

Thus, ethanol increases coronary blood flow in the nonischemic myocardium. However, in the acutely ischemic heart, ethanol produces an unfavorable redistribution of myocardial blood flow with flow in the nonischemic myocardium increasing, at least in part, at the expense of blood flow to ischemic myocardium, producing in effect a "coronary steal."

Alcohol is the oldest drug used to prevent and treat angina pectoris. Its putative benefits were first suggested by William Heberden[1] in his classic description of angina pectoris more than 200 years ago. Given the effects of ethanol on altering the perception of pain, its apparent favorable response in relieving angina pectoris might not reflect an improvement in myocardial supply-demand relations. Studies of the effect of ethanol on coronary blood flow have yielded conflicting findings. Some studies have found no change[2] or a decrease in coronary blood flow[3–5]; whereas other investigations[6–9] have demonstrated an increase. Moreover, even a demonstrable increase in total myocardial flow might not necessarily result in an increased blood supply to ischemic myocardium. Consequently, in this study we investigated the action of ethanol on myocardial flow in a canine model at blood levels of ethanol comparable with those found in man after the ingestion of several cocktails. The results indicate that, although ethanol increases blood flow to myocardium supplied by patent coronary arteries, flow to ischemic myocardium actually diminishes.

From The Brooklyn Hospital and State University of New York Downstate Medical Center, Brooklyn, New York. This work was supported by Grants-in-Aid from the Education Foundation of America, Westport, Connecticut, Fannie Ripple Fund, Morristown, New Jersey, Ambrose Monell Foundation, New York, New York and The Brooklyn Hospital, Brooklyn, New York. Manuscript received February 12, 1980; revised manuscript received July 10, 1980; accepted July 30, 1980.

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Methods

Experimental preparation: Thirty-five mongrel dogs that had fasted and weighed between 17 and 25 kg were anesthetized with sodium pentobarbital, 30 mg/kg, intravenously administered. No additional anesthesia was given during an experiment. All dogs were intubated and ventilated with a Harvard respirator. A left thoracotomy was performed and the heart was suspended in a pericardial cradle. Polyurethane catheters were positioned in the right atrium and descending aorta. Cannulas were placed in the left atrium and in the left ventricle through the apex. A Millar catheter-tipped micromanometer was positioned in the left ventricle through the apical cannula. To maintain catheter patency 4,000 units of sodium heparin was administered.

Measurements: Pressures were measured with a Statham 23dB strain gauge manometer with zero reference taken as the mid chest with the dog in a right lateral decubitus position. All pressure measurements were made over an entire respiratory cycle and the mean value of such a determination used. The first derivative of the left ventricular pressure pulse (dp/dt) obtained with the catheter-tipped micromanometer was computed continuously by a resistance-capacitance differentiating circuit and subsequently converted into mm Hg/s. The catheter-tipped micromanometer was calibrated in vivo using a fluid-filled catheter positioned in the left ventricle. Arterial pH, and partial pressures of oxygen and carbon dioxide were measured with a Radiometer Acid-Base Cart.

Myocardial blood flow was measured with 15 μ microspheres using the method of Domenech et al.[10]: Microspheres labeled with strontium-85, cerium-141, iodine-125 or chromium-51 were obtained from the 3M Company, Minneapolis in 1 millicurie vials suspended in 10 ml of 10 percent dextran, containing 0.5 percent of polysorbate (Tween 80®). After mechanical and ultrasonic agitation, 2 to 4 $\times 10^6$ microspheres were suspended in a 63 percent sucrose solution. These suspensions were agitated in an ultrasonic bath until used and then manually agitated until the moment of injection. Between 1 to 2 $\times 10^6$ microspheres in 5 ml of these suspensions were rapidly injected into the left atrium and the cannula was flushed with 5 percent dextrose in water over a 15 to 20 second period. Beginning 30 seconds before and continuing for exactly 2.5 minutes a reference blood sample was withdrawn from the arterial catheter at precisely 3.69 ml/min with a Harvard withdrawal pump. No electrocardiographic changes were observed during injection or withdrawal, and no appreciable hemodynamic alterations were produced. After the animal was killed with administration of potassium chloride, sections were obtained from the anteroapical, anterolateral and posterolateral segments of the left ventricle. Tissue was transversely divided into subepicardial, myocardial and subendocardial sections. All tissues were weighed to the nearest milligram, placed in glass tubes and counted for 5 minutes in a 3 inch (7.6 cm), well-type sodium iodide scintillation counter. Reference blood samples were divided into six aliquots. Appropriate energy windows and standard techniques were used for isotope separation.[10] To reduce further any error that might be introduced by contaminant activity contributed by accompanying isotopes and background, the order of isotopes was randomized for each experiment.

Flow to each area of myocardium (ml/min per 100 g) was calculated by using the formula:

$$QM = \frac{Qr \times Cm \times 100}{Cr \times Wt},$$

where Qm = myocardial flow (ml/min per 100 g), Qr = reference blood flow (ml/min), Cm = total counts in the myocardial sample, Cr = total counts in the reference sample and Wt = weight of the sample (g). Cardiac output (CO in liters/min) was calculated by using the formula

$$CO = \frac{Qr \times Ci \times 10^{-3}}{Cr},$$

where Ci = total counts of isotope injected. Calculation of flows was performed with an IBM Systems III computer. Ethanol blood levels were measured using the enzymatic method.[11]

Protocol: After the animals were prepared, control hemodynamic and myocardial blood flow determinations were made. In nine dogs ethanol (absolute dehydrated, USP), 1.7 g/kg body weight in a 25 percent (volume/volume) normal saline solution was continuously infused over 30 minutes. Five dogs received an equivalent volume of saline solution over the same period. Hemodynamic, myocardial blood flow and blood ethanol determinations were made after the infusion. In an additional 18 dogs, after control data were obtained, a coronary ligature was placed around the left anterior descending artery, first distal to a diagonal branch and then just proximal to the diagonal branch, as suggested by Harris et al.,[12] as a means of reducing the incidence of ventricular fibrillation. Ventricular fibrillation developed in three additional dogs. No attempt at defibrillation was made in these dogs and no antiarrhythmic agents were given to any dogs. After waiting 15 minutes for all ventricular premature complexes to disappear and hemodynamic variables to stabilize, hemodynamic and myocardial blood flow determinations were repeated. Nine dogs then received ethanol, 1.7 g/kg in saline solution delivered over 30 minutes, and nine dogs received an equivalent volume of saline solution delivered over the same period. After cessation of these infusions, hemodynamic, myocardial blood flow and blood ethanol determinations were made. The dogs were then killed with administration of potassium chloride.

Statistical analysis: Differences between groups were statistically analyzed by one way analysis of variance and Student's t test for unpaired data. Comparison of the changes in variables in the same group was performed using Student's t test for paired data. Values given are mean ± standard error of the mean. $p < 0.05$ was considered significant.

Results

Effects of Ethanol Before Coronary Ligation

Hemodynamic changes: Arterial pH, PO_2 and PCO_2 remained within physiologic limits. Only arterial pH changed after administration of ethanol, decreasing from an average of 7.41 ± 0.01 to 7.38 ± 0.01 (probability [p] <0.05). The average peak blood ethanol concentrations after 30 minutes of ethanol infusion was 225 ± 8 mg/dl (range 190 to 264) in nonischemic dogs. Ethanol produced an elevation of left atrial pressure (from 5.7 ± 0.6 to 7.7 ± 0.8 mm Hg, p <0.01) and venous pressure (from 4.1 ± 0.9 to 5.1 ± 0.8 mm Hg, p <0.01) and a slowing of heart rate (from 179 ± 8 to 171 ± 8 min^{-1}, p <0.001) (Fig. 1). Mean aortic pressure (127 ± 8 to 128 ± 9 mm Hg) and cardiac output (3.0 ± 0.2 to 2.8 ± 0.2 liters/min) (p = not significant [NS]) did not change. By contrast, an equivalent volume of saline produced no change in heart rate (160 ± 5 to 159 ± 8 min^{-1}), left atrial pressure (5.8 ± 1.3 to 6.4 ± 1.5 mm Hg), venous

pressure (5.7 ± 0.8 to 6.0 ± 0.8 mm Hg), mean aortic pressure (122 ± 9 to 118 ± 10 mm Hg) or cardiac output (2.8 ± 0.4 to 3.0 ± 0.3 liters/min).

Myocardial blood flow (Fig. 2): Average myocardial blood flow increased from 122 ± 5 to 143 ± 8 ml/min per 100 g ($p < 0.001$) after administration of ethanol. Saline solution produced no change in blood flow (117 ± 9 to 118 ± 9 ml/min per 100 g). Myocardial flow increased after ethanol in a transmural fashion. Subendocardial flow increased by 21 ± 6 from 130 ± 10 ml/min per 100 g ($p < 0.01$), myocardial flow by 24 ± 7 from 121 ± 9 ml/min per 100 g ($p < 0.02$) and subepicardial flow by 19 ± 6 from 115 ± 9 ml/min per 100 g ($p < 0.02$).

Effects of Ethanol After Coronary Ligation

Hemodynamic changes (Fig. 3): Occlusion of the left anterior descending artery produced an increase in left atrial pressure and a decrease in peak positive dP/dt. After an infusion of ethanol that produced an average peak concentration of 201 ± 13 mg/dl (168 to 288) at 30 minutes, left atrial pressure increased from 6.3 ± 0.6 to 7.4 ± 1.4 mm Hg ($p < 0.05$) but peak dP/dt declined from 2596 ± 284 to 2276 ± 257 mm Hg/s (p = NS). Heart rate (156 ± 9 to 163 ± 7 min^{-1}) and mean aortic pressure (115 ± 8 to 115 ± 6 mm Hg) did not change. By contrast, saline solution produced no change in left atrial pressure (8.6 ± 0.6 to 8.6 ± 0.7 mm Hg), heart rate (160 ± 9 to 156 ± 8 min^{-1}), mean aortic pressure (112 ± 9 to 111 ± 13 mm Hg) or peak positive dP/dt (2766 ± 339 to 2802 ± 267 mm Hg/s). Peak positive dP/dt increased in seven of the nine dogs receiving saline after coronary ligation, whereas only two of the nine dogs receiving ethanol after coronary ligation showed an improvement in this variable even though left atrial pressure had risen significantly.

Myocardial blood flow (Fig. 4): In dogs receiving saline solution, myocardial flow did not change significantly in either the ischemic (20 ± 7 to 16 ± 5 ml/min per 100 g) or nonischemic zone (122 ± 13 to 130 ± 14 ml/min per 100 g). Dogs receiving ethanol showed a significant redistribution of myocardial blood flow ($F = 6.46$, $p < 0.001$). Blood flow in the ischemic zone decreased from 30 ± 6 to 20 ± 5 ml/min per 100 g ($p < 0.02$) whereas flow in the nonischemic zone increased from 118 ± 7 to 148 ± 15 ml/min per 100 g ($p < 0.005$). Figure 5 illustrates the changes in distribution of myocardial blood flow in the ischemic heart after administration of ethanol. The decrease in blood flow is shown to occur in a transmural fashion in the ischemic zone.

In Figure 6 changes in myocardial blood flow after administration of ethanol are considered as a function of the severity of myocardial ischemia. Myocardial tissue demonstrating myocardial perfusion equal to or greater than 80 percent of preligation levels showed a significant increment in blood flow after ethanol, by 31 ± 5 ml/min per 100 g ($p < 0.001$). The increment in blood flow was greatest in the subendocardium, increasing by 42 ± 10 ml/min per 100 g ($p < 0.001$) and least in the subepicardium increasing by 17 ± 6 ml/min per 100 g ($p < 0.01$). By contrast, myocardial tissue having an average blood flow level equal to or less than 60 percent of preligation values showed a significant decline in myocardial blood flow. In myocardium with an average flow ranging between 61 to 79 percent of preligation values, subendocardium showed an increase in flow whereas the subepicardium showed a decrease in flow, by 33 ± 12 ml/min per 100 g ($p < 0.05$).

Thus, ethanol increased myocardial blood flow in a transmural fashion in the nonischemic heart. In a heart that had an acute occlusion of a coronary vessel, blood flow increased in nonischemic tissue but decreased in ischemic tissue. The increment of blood flow appeared to be greatest in the subendocardial nonischemic zone

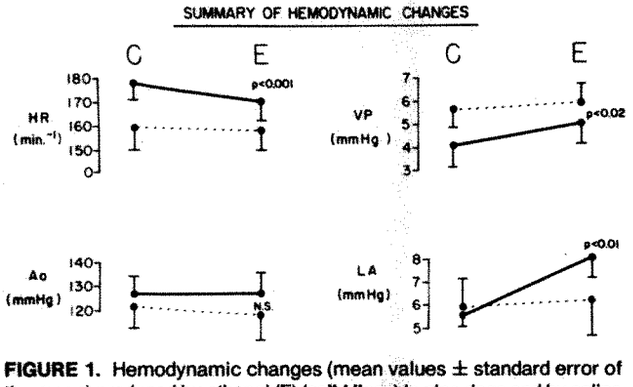

FIGURE 1. Hemodynamic changes (mean values ± standard error of the mean) produced by ethanol (E) (**solid lines**) in nine dogs and by saline solution (**interrupted lines**) in five. Ethanol produced a decrease in heart rate (HR) and an increase in venous pressure (VP) and left atrial pressure (LA) but no change in mean aortic pressure (Ao). C = control; N.S. = not significant; p = probability.

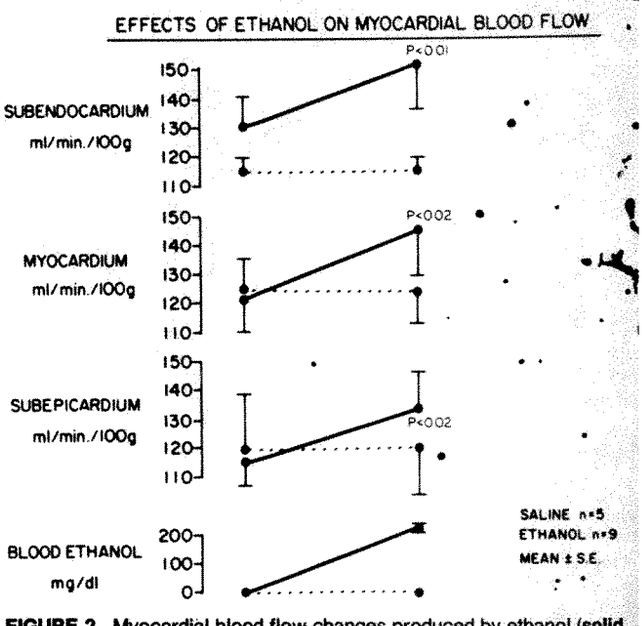

FIGURE 2. Myocardial blood flow changes produced by ethanol (**solid lines**) and saline solution (**interrupted lines**). Ethanol produced a transmural increase of blood flow whereas saline solution produced no change. n = number of studies; S.E. = standard error.

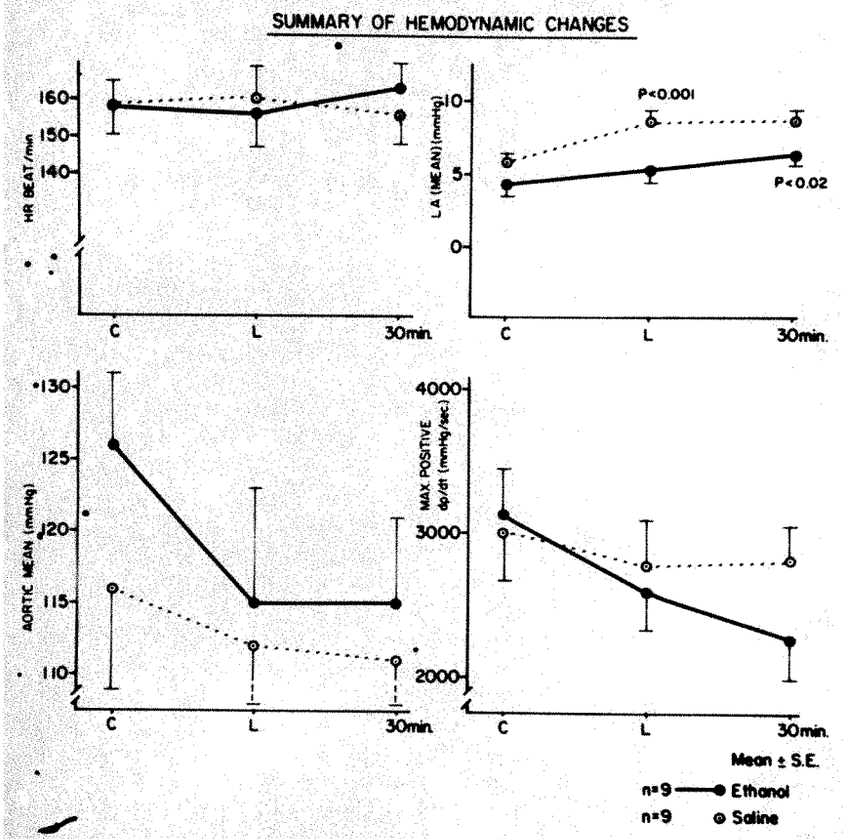

FIGURE 3. Hemodynamic changes produced by coronary arterial ligation (L) and after 30 minutes of saline or ethanol infusion. C = coated; MAX. = maximal; other abbreviations as in Figure 1.

whereas the decrease in flow appeared to be greatest in the subepicardial ischemic zone.

Discussion

Effects of ethanol on coronary blood flow: Within physiologic limits in the intact heart, the coronary circulation is autoregulatory.[13] Because ethanol has a complex array of hemodynamic and metabolic effects, it should not be surprising that conflicting observations have been made on the effects of ethanol on myocardial blood flow. Ethanol[6] and its metabolite, acetaldehyde,[14] both have direct coronary vasodilatory effects. The depressant actions of ethanol[5,9,15] and the catecholamine-releasing properties of both ethanol[16] and acetaldehyde[17] can also produce changes in myocardial blood flow by affecting myocardial oxygen consumption. Previous studies have differed in the animals used, the dosage or rate (or both) of ethanol administration, the types of anesthesia and also the methods used for measuring changes in coronary blood flow. Given these

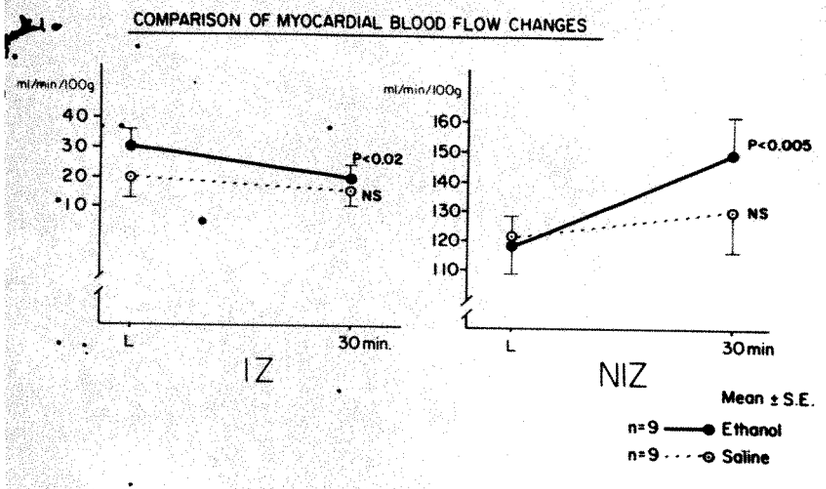

FIGURE 4. Myocardial blood changes produced by ethanol and saline solution in ischemic zone (IZ) and nonischemic zone (NIZ) of myocardium. Ethanol (**solid line**) reduced flow in ischemic tissue and increased flow in nonischemic tissue. Saline solution (**broken line**) did not produce a significant change.

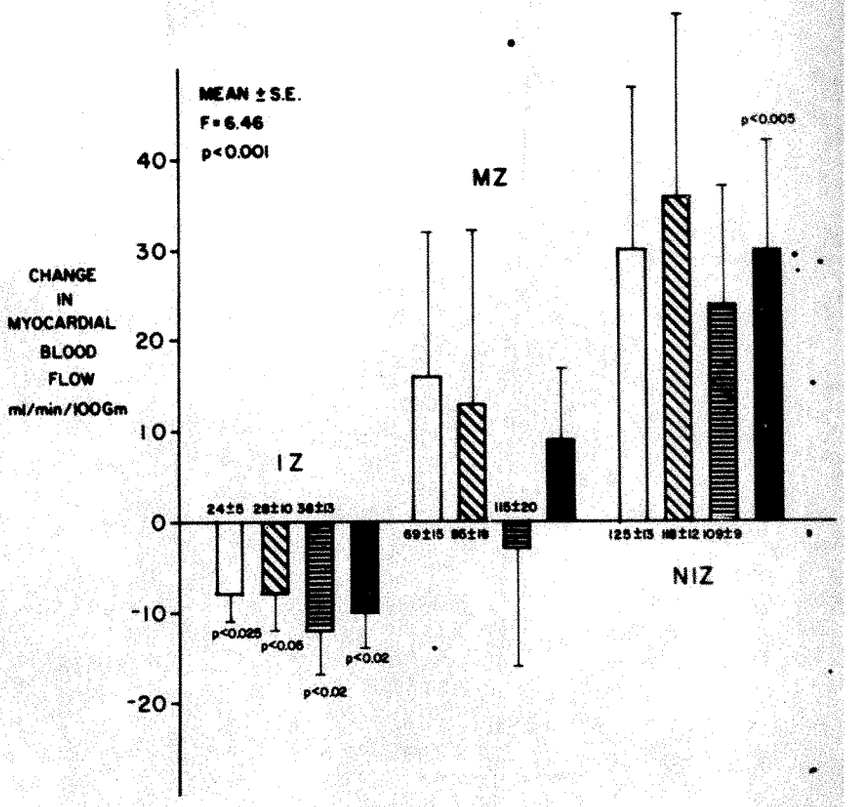

FIGURE 5. Redistribution of blood flow produced by ethanol. Ischemic (IZ), adjacent to ischemic (MZ) and nonischemic (NIZ) zones, and subendocardial (**white bars**), myocardial (**diagonal lines**), subepicardial (**horizontal lines**) and average transmural (**black bars**) flows are compared. **Values at base of bars** indicate myocardial flow after coronary ligation; **bars** indicate changes produced by ethanol.

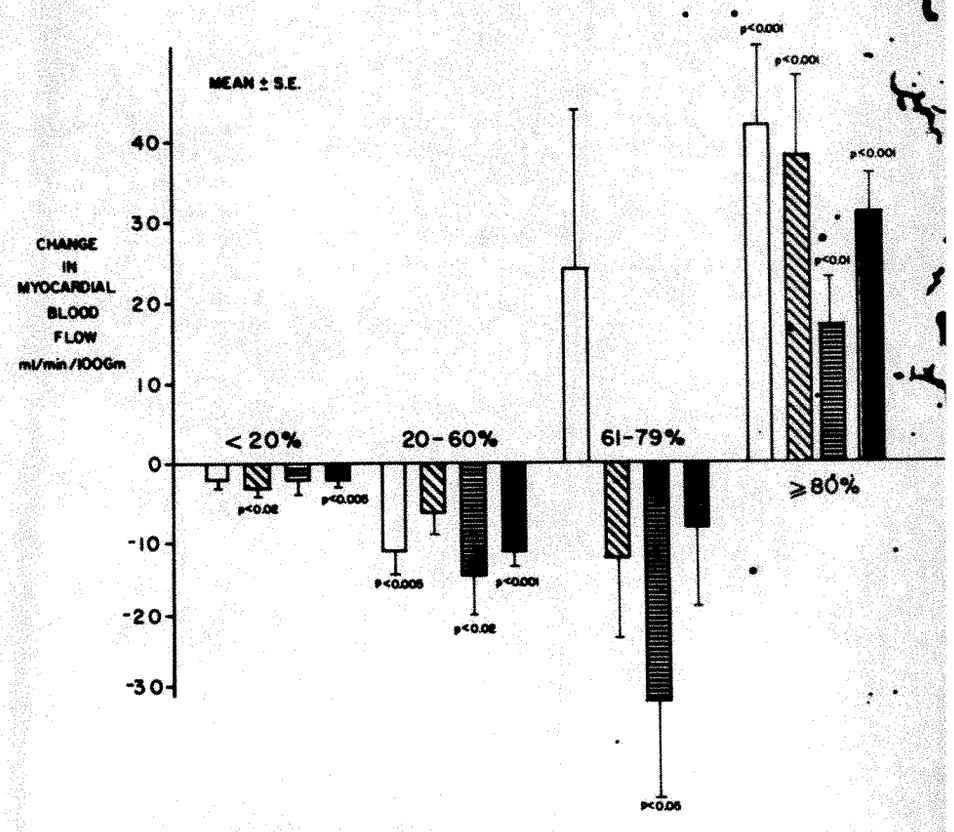

FIGURE 6. Effect of ethanol on myocardial blood flow displayed as a function of tissue flow (expressed as a percent of preligation flow before ethanol administration). Subendocardial (**white bars**), myocardial (**diagonal lines**), subepicardial (**horizontal lines**) and average transmural (**black bars**) flows are compared.

differences, some investigators[6–9] reported an increase in coronary flow after ethanol administration, some[3–5] found a decrease, others[2] observed no change, and one group[18] found no change at a low blood level of ethanol but an increase in blood flow at concentrations approximating the levels found in our study.

In our study, at blood levels that would produce alcoholic intoxication in man, ethanol was shown to increase myocardial blood flow in the neurally intact anesthetized dog. In these experiments an increase in flow occurred at a time when mean aortic pressure and cardiac output had not changed, left atrial pressure had increased and heart rate had slowed. Although myocardial oxygen consumption and coronary sinus oxygen content were not measured, in a series of similar experiments[9] that produced comparable hemodynamic effects but a more variable response on heart rate and left atrial pressure, myocardial oxygen consumption and coronary venous oxygen levels were found to increase after ethanol administration.

Ethanol and myocardial blood flow in ischemic versus nonischemic myocardium: Because a substance that increases total coronary blood flow might not necessarily result in an increase in blood flow to ischemic myocardium under similar experimental conditions, the effects of ethanol on myocardial flow after coronary ligation were studied. Although blood flow in nonischemic myocardium increased following ethanol administration, in the ischemic myocardium it declined. The decline in perfusion was observed in myocardium having an average blood flow equal to or less than 60 percent of preligation levels. Blood flow declined in a transmural fashion in the ischemic myocardium. However, the pattern of flow in nonischemic areas suggested that the maximal increment of flow occurred in the subendocardium whereas the maximal decrease occurred in the subepicardium. Thus, ethanol appears to produce an unfavorable redistribution of blood flow in the ischemic heart, with blood flow increasing in nonischemic myocardium, in part at least, at the expense of flow to ischemic myocardium, in effect producing a "coronary steal."

Potential limitations of study: Our observations must be viewed in the context of the experimental design. One limitation is that the dogs were studied after they had been anesthetized with sodium pentobarbital. However, in a study of conscious dogs ethanol was found to increase coronary blood flow.[8] It would thus seem plausible to adduce from our data that ethanol is likely to produce a "coronary steal" in the conscious dog after coronary ligation. A second limitation of the study is that ethanol was infused intravenously rather than imbibed. The failure of a saline infusion to produce the changes observed would argue in favor of ethanol or its metabolite, or both, as the agent responsible for the changes observed rather than the saline solution or the volume administered itself. Furthermore, measurement of acetaldehyde levels during ethanol infusion under similar experimental conditions[9] demonstrated that ethanol is metabolized in the dog in a similar fashion to that observed in human beings given an infusion of ethanol.[19]

A third concern is the canine response to an acute coronary ligation. In dogs, unlike human beings, coronary collateral vessels rapidly develop after an acute coronary ligation. Because most of these vessels appear within a few minutes after ligation[20], we attempted to mitigate the effects of this response by allowing 15 minutes to elapse before obtaining control data. Also, the effect of ethanol on perfusion to ischemic myocardium resulting from an acute occlusion might be different from the effect of ethanol on myocardial ischemia due to coronary stenosis with superimposed coronary spasm. Finally, the blood levels of ethanol obtained in our study, while within the range observed in human beings with acute alcohol intoxication, are in excess of those that would be seen with more casual use of alcoholic beverages. It is possible that smaller quantities ingested and producing lower blood levels might have had different effects on the ischemic myocardium.

Clinical significance: This study suggests another possible adverse effect of ethanol in organic heart disease. It has previously been shown that ethanol depresses cardiac function in patients with heart failure.[21] Ethanol may also adversely affect myocardial demand-supply relations in ischemic myocardium. Clinical studies[23] have demonstrated that angina pectoris and the abnormal electrocardiographic response to exercise are not favorably affected by ingestion of alcohol[22] and that myocardial ischemia might even occur sooner and with more exaggerated S-T segment depression. Moreover, a toxic myocardial infarction has been described in alcoholic patients not having coronary heart disease.[24] It is possible that a "coronary steal" produced by ethanol might contribute to these occurrences. Although several epidemiologic surveys[25–27] suggest that ethanol may have a protective effect on atherogenesis, our study suggests that ethanol ingestion should at least be limited in patients with coronary heart disease.

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Derivation of Systolic Time Intervals From Doppler Measurement of Temporal Arterial Blood Flow

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The carotid pulse method of recording systolic time intervals is limited by significant motion-induced artifact, making it unsuitable for studying patients during exercise. As an approach to overcoming this limitation, a new method utilizing the blood velocity profile of the superficial temporal artery measured by Doppler ultrasound has been developed. When compared with the values obtained from the conventional carotid pulse method, Doppler-derived left ventricular ejection time and preejection period showed excellent correlation (r = 0.99 for both) and the Doppler-derived measurements showed little intra- or interobserver variability. Studies performed during treadmill exercise showed that in 8 of 10 subjects, suitable tracings could be recorded through stage 3 of the Bruce protocol, confirming the enhanced stability of the technique compared with the carotid pulse method.

Over the past decade, systolic time intervals have frequently been used as an approach to the noninvasive evaluation of left ventricular function.[1–13] The carotid pulse tracing has traditionally been the basis for determination of left ventricular ejection time and the preejection period. However, the unstable relation of the transducer to the underlying carotid artery is a significant limitation of this technique; even minor movement of the neck muscles can introduce considerable artifact into the tracings. As a result, the diagnostic application of systolic time intervals to the evaluation of left ventricular responses during physical exertion has been difficult using the carotid pulse method.

In an effort to overcome this limitation, we developed a new method of deriving systolic time intervals, by utilizing the blood flow profile of the superficial temporal artery as measured with Doppler ultrasound. This report outlines our initial experience with the technique.

Methods

Recording technique: A commercially available Doppler flow probe (Parks Electronics, Beaverton, Oregon) consisting of miniature transmitting and receiving crystals embedded in a 1.5 by 2 cm flat plastic housing (Fig. 1, top) was used to generate a velocity profile suitable for derivation of systolic time intervals. One crystal transmits an ultrasonic wave (9.7 megahertz) that is reflected from moving red blood cells; the reflected signal is frequency-shifted in direct proportion to the blood flow velocity and is received by the second crystal for further processing. The transducer is positioned by palpating the superficial temporal arterial pulse over which the transducer is then placed (Fig. 1, bottom), oriented with the groove on the transducer surface immediately over the artery and parallel to its course to minimize arterial compression. The transducer is next secured in place with an elastic headband; final positioning is accomplished with the aid of audio and visual oscilloscopic feedback to insure an optimal flow tracing.

The transducer is interfaced with a continuous wave Doppler flowmeter (Parks Electronics model 806) that detects the magnitude and direction of the frequency shift of the signal reflected from moving red blood cells and electrically transforms these data into a voltage proportional to blood flow velocity that is then displayed on an oscilloscopic recorder for permanent copy. Calibration of ab-

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solute velocity was not employed because relative changes in velocity were sufficient for purposes of this study.

To validate systolic intervals derived by this technique, we obtained simultaneous recordings of the ipsilateral carotid pulse employing an air-coupled Statham P23Db transducer. A phonocardiogram was obtained with a contact microphone (Cambridge 3040500) positioned to optimize recording of the aortic component of the second heart sound. Carotid systolic time intervals, preejection period and left ventricular ejection time were derived by the method of Weissler et al.[1] For consistency, the right temporal artery and right carotid pulse tracings were compared in all cases.

Study subjects: Twenty normal subjects aged 21 to 35 years were studied using these techniques in the supine position; 10 were also studied while sitting, standing and standing immediately after completion of treadmill exercise. We also applied this method to 10 normal volunteers exercising through stage 3 of the Bruce protocol. Reported values are an average of systolic time interval determinations from five measured beats. The results of carotid and temporal arterial Doppler systolic time intervals were compared using linear regression analysis.

Results

Comparison of Doppler and carotid pulse method: The temporal arterial velocity profile demonstrates a discrete point of upstroke and a sharp incisura (Fig. 2) analagous to the carotid waveform but with a longer pulse transmission delay. Left ventricular ejection time was determined as the interval in milliseconds from the point of rapid upstroke to the incisura. The preejection period was then derived by subtracting the left ventricular ejection time from the interval Q-A_2 (Q wave to aortic component of second heart sound).

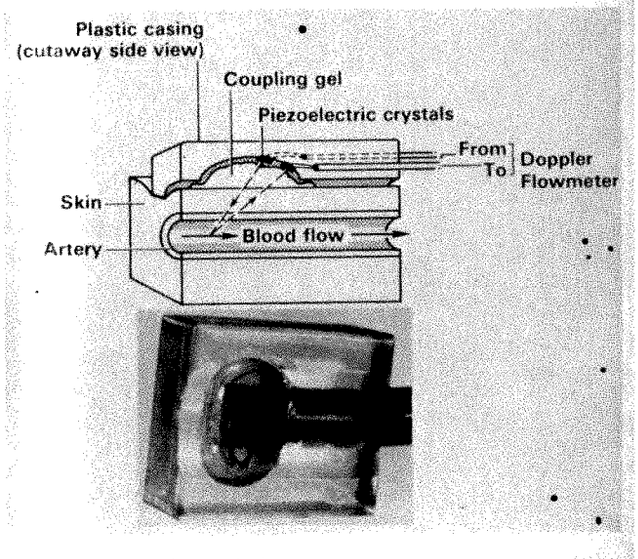
When compared with the values obtained from the conventional carotid pulse method, Doppler-derived left ventricular ejection time (LVET) and preejection period (PEP) demonstrated excellent correlation (Fig. 3) with regression equations as follows:

$$LVET_D = 0.98\ LVET_c + 4.9\ (r = 0.99)$$

$$PEP_D = 1.05\ PEP_c - 5.4\ (r = 0.99)$$

where D = Doppler and c = carotid method. The maximal difference between left ventricular ejection time measured with the Doppler and carotid methods for any individual patient was 10 ms, with a mean absolute difference of 2.9 ms (standard deviation 2.4 ms). As a result of the effects of the different positions used on systolic time intervals, a wide range of values for both the left ventricular ejection time and the preejection period was available for comparison.

Reproducibility of Doppler determinations: To assess the reproducibility of Doppler determinations of the left ventricular ejection time, duplicate measurements were made on the tracings of 12 subjects studied in the supine position. Interobserver variability was determined by having a second observer measure the left ventricular ejection time from the same tracings used for the initial data without constraint regarding complexes chosen for the measurement. Intraobserver variability was assessed by having one observer record systolic time intervals from the same tracings in each of the 12 subjects on two different occasions. The data were then compared using the t test and linear regression analysis. For interobserver data, the mean difference in left ventricular ejection time was 1.4 ms (range 0 to 7, standard deviation 3.7) with a correlation coefficient of 0.98. For intraobserver data, the mean difference was 0.2 ms (range 0 to 5, standard deviation 2.8) with a correlation coefficient of 0.99. In neither case was the difference between measurements statistically significant by the t test ($p > 0.1$).



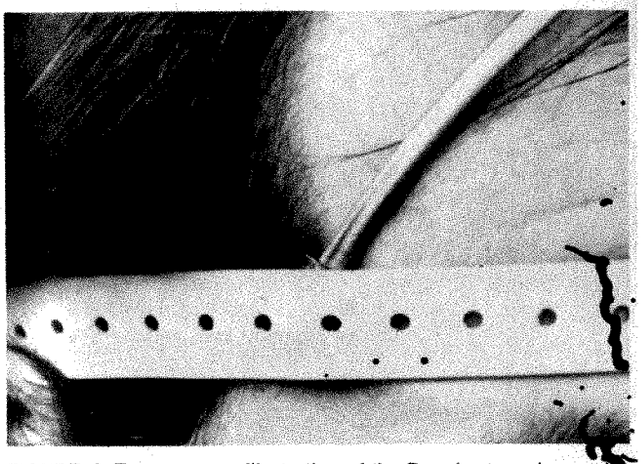


FIGURE 1. Top, cutaway illustration of the Doppler transducer with close-up view of the actual transducer. **Bottom,** close-up photograph of a subject with the transducer positioned over the temporal artery and secured with the elastic headband.

In studies conducted during treadmill exercise, tracings of 8 of the 10 subjects were suitable for measurement through stage 3 of the Bruce protocol. Figure 4 is a representative tracing of temporal arterial Doppler flow velocity obtained from one subject during stage 3 at a heart rate of 145 beats/min. The sharp upstroke and incisura remain easily identifiable at this point.

Discussion

Recording of the carotid pulse wave for the derivation of external systolic time intervals is somewhat restricted in application by cervical anatomy. The overlying soft tissue and muscle occasionally prevent acquisition of

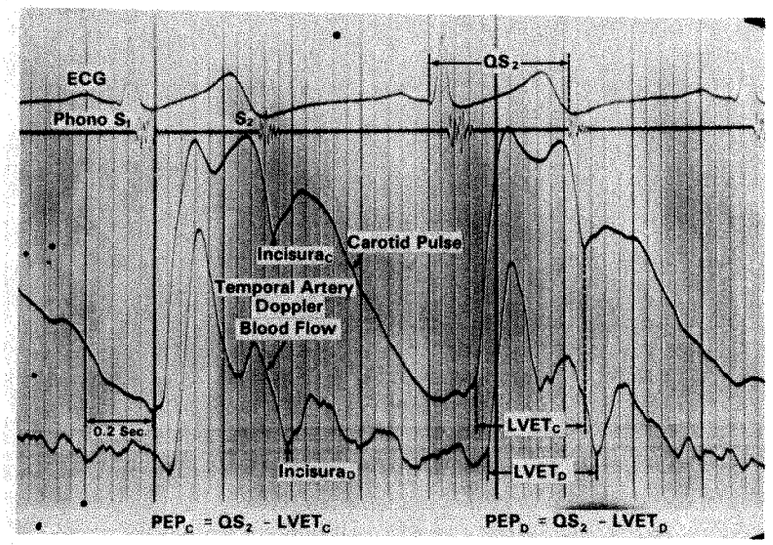


FIGURE 2. Unretouched recording of electrocardiogram (ECG), phonocardiogram (phono), carotid pulse and temporal arterial blood velocity profile indicating points of measurement. Note the sharp upstroke and incisura of the velocity profile. C = carotid pulse measurement; D = Doppler measurement; LVET = left ventricular ejection time; PEP = preejection period.

a suitable tracing, and significant activity of the neck musculature such as that seen with respiratory distress or exercise has significantly limited application of systolic time intervals in these situations. For example, most previously reported responses of systolic time intervals to exercise have compared values obtained before and after (but not during) exercise or, if done during exercise, have generally been limited to healthy young persons studied in the supine position.[2,3,5–11,13] Alternative techniques have been described, including finger plethysmography, ear densitometry and impedance cardiography,[14,16] but each of these methods has the drawback of requiring either extrapolation or further electronic processing (usually differentiation) of the raw signals to identify the timing of the aortic incisura. The impedance cardiogram was found by Balasubramanian et al.[16] to be unsuitable for use in treadmill exercise and in all but mild sitting bicycle exercise because of motion-induced artifact.

Correlation of systolic time intervals derived by temporal arterial velocity and conventional carotid methods: Velocity curves in previous reports[17,18] relating to blood flow and acceleration in the aorta suggested that the velocity profile might provide the nec-

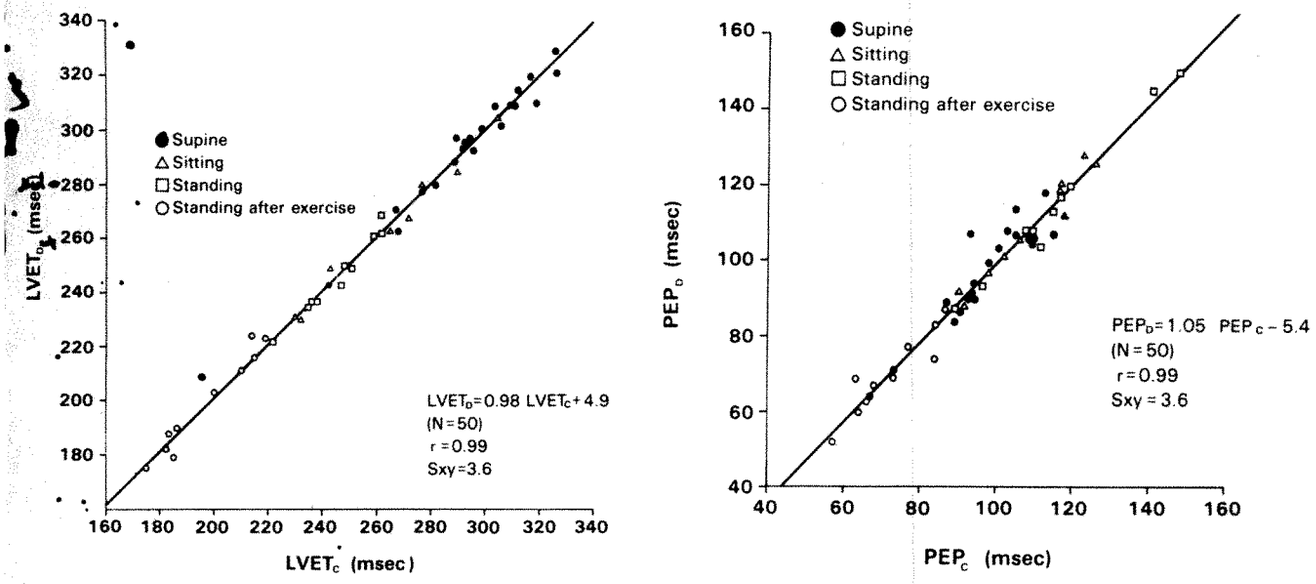


FIGURE 3. Graphic representation of the correlation between Doppler (D) and carotid (C) measurements of left ventricular ejection time (LVET) (**left**) and preejection period (PEP) (**right**). Sxy = standard error of the estimate.

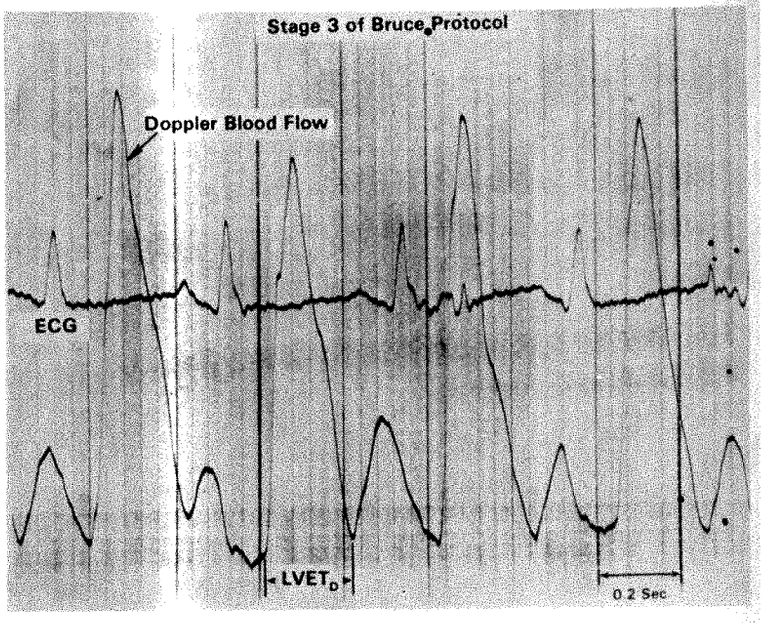


FIGURE 4. An example of a temporal arterial blood velocity recording obtained during stage 3 of the Bruce protocol. Note the clear definition of upstroke and incisural points. ECG = electrocardiogram; $LVET_D$ = left ventricular ejection time obtained with Doppler method.

essary information for derivation of left ventricular ejection time. We chose the superficial temporal artery because it is easily accessible, does not vary in its relation to overlying tissues and seemed unlikely to be subject to muscle contraction artifact. Our results demonstrated that the velocity profile of this artery may be used as an accurate basis for calculating systolic time intervals, the results correlating highly with values obtained by the conventional carotid method.

Requisite to this correlation is a similar relation between the pulse transmission times: $upstroke_{carotid}$ to $upstroke_{Doppler}$ and $incisura_{carotid}$ to $incisura_{Doppler}$. Any difference in these intervals would result in a difference of calculated ejection times, which may be expressed as

$$LVET_D - LVET_c = \Delta t_i - \Delta t_u,$$

where c = carotid method; D = Doppler method; Δt_i = interval between incisuras; Δt_u = interval between upstrokes; and LVET = left ventricular ejection time. Despite the high correlation coefficient and the small mean absolute difference in ejection time, the regression equation implies that some systematic difference may exist. To estimate the magnitude of such a difference (either constant or as a function of ejection time) over the range studied, direct substitution of sample values may be made in the regression equation. For a carotid-derived ejection time of 180 ms (the lower end of the range studied), the calculated value for the Doppler-derived ejection time would be 181.3 ms. For a carotid-derived value of 330 ms (the upper end of the range studied), the Doppler-derived value would be 328.3 ms. Therefore, there may be some systematic difference between the two methods, in that the Doppler-derived value is slightly greater for very short ejection times, whereas the carotid-derived value is slightly larger for longer ejection times. (This would imply that the pulse transmission time between incisuras is slightly greater than that for the upstrokes for short ejection times and smaller for very long ejection times.) However, the estimated difference in the range studied is very small and probably within the range of measurement error for carotid-derived ejection time.[19]

Advantages of the method: The major advantage of this new technique is reduction in motion artifact as demonstrated by our ability to record satisfactory tracings in 8 of 10 subjects exercising through stage III of the Bruce treadmill protocol. (In contrast, we were unable to record systolic time intervals using the carotid pulse method during stage I of the Bruce protocol.) The specific source of the artifact that obscured the upstroke and incisural points in two of our subjects (and affected others to a lesser extent) is not entirely clear. Apart from the obvious possibility of motion of the transducer itself, it is likely that the up and down motion of the body during running causes an acceleration and deceleration of the column of blood in the aorta that is superimposed on the aortic blood velocity and transmitted to the temporal blood flow as well. Beyond stage III of the Bruce protocol, most subjects must run, and the exaggerated "bobbing" motion makes even this method impractical. In practice, this may not be an important limitation in the testing of patients. For example, more than 80 percent of patients in our laboratory found to have significant coronary artery disease on cardiac catheterization studies are not able to exercise beyond stage III. The technique is simple and the flow curves provide discrete points for measurement, thus averting the need for extrapolation or further processing. This method could easily be adopted by any laboratory with Doppler vascular blood flow equipment. Recent work

by Goldwater et al.[20] supports the accuracy of this technique in studying patients under a variety of conditions affecting ejection time.

Future applications: Another aspect of this technique, which awaits further evaluation, is the potential for use of the additional information provided by the velocity profile. Ejection velocity and acceleration data permit more complete characterization of ventricular function than systolic time intervals alone. Previous studies employing both invasive and noninvasive techniques[17,18,21–27] have shown flow indexes in the aorta and more peripheral vessels to be useful in characterizing left ventricular function and evaluating valvular heart disease. Further experience and correlative studies will be necessary to define completely the usefulness of this technique in such applications.

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Predicting Cardiac Morbidity Based on Risk Factors and Coronary Angiographic Findings

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A cohort of 189 men was followed up for 1 year after performance of coronary angiography and determination of risk factors to ascertain which risk factors or clinical and laboratory findings could aid in predicting the patients who would have a substantial cardiac morbid event. Data on clinical signs and symptoms, psychosocial assessments, angiographic findings and presence of standard risk factors for coronary artery disease were collected in each case.

Twenty-five percent of the men experienced a substantial cardiac morbid event (hospitalization, myocardial infarction, resuscitation or death). With or without inclusion of the patients who underwent surgery, discriminant analysis equations were successful in predicting morbidity on the basis of risk factor data. For the whole sample such analysis was significant at $p < 0.00005$ and accurately predicted the fate of 78 percent of the subjects. With exclusion of the surgically treated patients, the discriminant analysis accurately predicted future morbidity 83 percent of the time ($p < 0.0001$). The following risk factors for increased morbidity were common to both analyses: severity of angina, history of myocardial infarction, family history of heart disease, fatigue and absence of type A behavior.

In addition to diagnosis, cure or palliation, patients often see physicians for an assessment of their prognosis. However, the estimation of prognosis in ischemic heart disease is a complicated matter wherein many factors must be considered. Changes in medical or surgical treatment, advances in the knowledge of factors conveying risk for illness, advances in understanding the pathophysiology of these risk factors, as well as the patient's life style and unknown factors complicate any effort to prognosticate accurately.

In earlier work we[1–4] reported our efforts to utilize a broad range of risk factors for coronary artery disease to assess their relation to the extent of such disease found on angiography. This study extends the findings of our earlier work by examining prospectively the subsequent development of cardiac morbid events in patients who have undergone careful risk factor determination and coronary angiography. A cohort of patients was followed up for 1 year to ascertain which risk factors or clinical and laboratory findings could aid in predicting the onset of later morbidity. Factors ranging from clinical observations on the patient's physical examination to data from laboratory studies, psychometric tests and interviews and, finally, coronary angiography were included in each person's assessment. Although some excellent studies[5,6] have related various individual risk factors and combinations to the later incidence of morbid events, we believe that this broad-based approach may provide additional information.

Method

Study patients: Patients were eligible for study who underwent cardiac catheterization primarily because of symptoms of coronary artery disease. Men between the ages of 18 and 70 years were included in this study; the average age

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was 50 years. Patients were excluded from the study if they underwent angiography for valvular heart disease, had any severe illness other than heart disease that might influence their clinical course during the follow-up period, or were in such critical condition that interviews were not feasible.

In a 2 year period, 216 men were approached for enrollment in this study. Only 12 did not participate—3 because the primary physician advised against participation, 6 because the patient himself declined to participate and 3 because they were found ineligible; thus, 204 men were studied.

Risk factors studied: Table I lists the risk factors studied. Information on these factors was obtained before angiography through patient interviews and chart reviews. Tension, depression, anger and fatigue were measured with the Profile of Mood States.[7] Denial was measured with the Hackett-Cassem semistructured interview.[8] Type A personality was measured with the Jenkins Activity Survey (JAS).[9] Stress accumulation was measured with a 42 item Schedule of Recent Events (SRE).[10] The patient was considered to have a family history of heart disease if a parent or sibling had had heart disease before age 60 years. Diabetes was considered present if the patient had been treated with an antidiabetic agent; it was considered possibly present if he had a history of an abnormal glucose tolerance test or had been told by a physician that he needed to be on an antidiabetic diet. Smoking was measured in pack-years. Electrocardiograms were graded as normal or abnormal using the criteria of Peel et al.[11]; Q waves were scored as present or absent. Severity of angina was graded according to New York Heart Association criteria.[12] Cholesterol and triglyceride values were measured as fasting levels. The Coronary Prognostic Index was derived by the method of Peel et al.[11]

Coronary angiography: The majority of patients underwent angiography at a time remote from myocardial infarction. Cardiac catheterization was performed by the Judkins or Sones technique. Vessels were considered significantly narrowed if they showed 50 percent or greater narrowing of diameter. Vessel disease was graded from 0 (no significant vessel disease) to 4 (significant vessel disease in the left main coronary, left anterior descending, left circumflex and right coronary arteries). Angiography was performed and X-ray films interpreted by physicians unaware of the risk factor determinations for this research. Although all patients were presumed to have coronary artery disease, approximately 15 percent were found to be free of any major coronary artery disease on angiography.

Follow-up: Follow-up contact was attempted 1 year after coronary angiography. Follow-up interviews were conducted either in person or by telephone; if the patient had moved out of the country, information was gathered from written questionnaires. One hundred eighty-nine of the 204 patients or their families were contacted and completed the follow-up interview. Seventy-nine men underwent coronary bypass surgery in the follow-up period. Because of the possibility that surgical treatment would alter the relation between incoming risk factors and the developing morbidity, the data were analyzed in two ways— (1) considering the total population of 189 men, and (2) considering only the 110 nonsurgically treated men.

Morbid events were classified as follows: No morbid event, emergency room visit because of cardiac problem, hospital admission because of cardiac problem, myocardial infarction, resuscitation or death. If bypass graft surgery was performed within 4 months of angiography, the hospitalization for surgery was not counted as a morbid event. It is our impression that bypass surgery performed later than 4 months after angiography is usually motivated by a deterioration in the patient's condition; in such cases hospitalization was counted as a morbid event. Table II lists the morbid event experience accumulated by our cohort. Each patient was assigned a morbidity category corresponding to the worst morbid event occurring in the 1 year follow-up period. Thus, a patient who had two emergency room visits and one hospitalization was assigned a morbidity score corresponding to a hospitalization. In an effort to maximize the amount of agreement about what constitutes a "morbid event," emergency room visits were not considered "substantial morbid events." Approximately 25 percent of the sample accrued a substantial morbid event (worse than an emergency room visit) in the follow-up period.

Statistical analysis: The association of the later development of morbidity with combinations of earlier determined risk factors and angiographic findings was examined with discriminant analysis.[13] This statistical procedure utilizes as few variables as possible and weights them to derive the optimal polynomial equation that separates subjects into two distinct groups. In this case the two groups were: (1) patients who accumulated a substantial morbid event, or (2) patients who accumulated no morbid event other than emergency room visits. By considering the interaction between variables, this technique pares the list to an optimal combination of variables predictive of who would have a substantial morbid event.

TABLE I

Risk Factors Considered

Angiographic extent of coronary artery disease
Serum cholesterol
Serum triglyceride
Depression
Anger
Fatigue
Type A behavior
Denial
Stress
Abnormal electrocardiogram
Diabetes
Family history of heart disease
Severity of angina
Q waves on electrocardiography
Tension
Peel score
History of past myocardial infarction
Blood pressure
Age
Smoking

TABLE II

Morbid Events Accumulated in 1 Year by All Cohort Patients*

	Cases	
	n	%
No morbid event	126	(66)
Emergency room visit for cardiac problem	15	(8)
Hospitalization for cardiac problem	30	(16)
Myocardial infarction	9	(5)
Resuscitation	2	(1)
Death	8	(4)

* Each patient is classified according to his most serious morbid event.

Results

We used a stepwise discriminant analysis to search for the optimal combination of variables listed in Table I that would differentiate between patients experiencing a substantial morbid event and patients without a substantial morbid event. Table III summarizes these findings. For the whole group the discriminant analysis was highly significant ($p < 0.00005$), accurately predicting the fate of 78 percent of the men. The most important variables (in decreasing order of importance) were: severity of angina, history of past myocardial infarction, family history of heart disease, fatigue, absence of type A personality, depression and a low serum cholesterol level.

After exclusion of the surgically treated patients, discriminant analysis was still highly significant ($p < .0001$), accurately predicting the fate of 83 percent of the men. The most important variables (in decreasing order of importance) were severity of angina, history of past myocardial infarction, family history of heart disease, presence of electrocardiographic Q waves, age, stress, absence of type A personality, low level of acknowledgment of anger, and fatigue. The number of coronary vessels found diseased on angiography was not a discriminating variable for either of the two equations.

Discussion

Limitations and advantages of study: This is a small sample from a highly selected group—patients undergoing coronary angiography at a university teaching hospital. These limitations must be kept in mind before extrapolating the findings to the larger population of patients with coronary artery disease. Nevertheless, the study presents two advantages. First, it is a prospective study with all risk factors and clinical findings determined before the occurrence of morbid events. Second, it is intentionally broad-based to include clinical findings, standard epidemiologic risk factors, psychosocial risk factors and, finally, angiographic findings in an effort to utilize the maximal amount of information relevant to predicting the patients' future.

Because our sample size was limited and the duration of our follow-up period was only 1 year, we grouped various untoward clinical events together under the heading of "morbid events." There were too few cases of specific morbid events (such as death) to warrant examining these events separately. By grouping these events together we were unable to examine whether various risk factors were associated with a particular outcome but, we were able to discern which factors were related to an assortment of "bad outcomes."

Medically versus surgically treated patients: We explored the relation between risk factors and morbidity, both with and without the surgically treated patients. Excluding surgically treated patients would introduce a bias in the study by excluding approximately 40 per cent of the follow-up sample. However, including these patients introduces another bias in that surgical treatment is likely to alter substantially the relation between incoming risk factors and developing morbidity. As Table III demonstrates, if risk factors are considered one can impressively predict future morbidity whether or not surgically treated patients are excluded. Thus the equation derived from the entire sample of 189 patients achieved a significance of $p < 0.00005$ and accurately predicted future morbidity 78 percent of the time, and that derived from the 110 medically treated men was significant at $p < 0.0001$ and predicted the fate of the cohort with 83 percent accuracy.

In both analyses the three most important variables were identical. These were: severity of angina, history of myocardial infarction and a family history of heart disease. Although their exact order of importance differed in the two analyses, fatigue and the absence of type A behavior were also key discriminatory variables.

Type A behavior as a risk factor: At first glance these findings seem to contradict the reports[14,15] relating type A behavior to both new and recurrent coronary events. In the setting of fatigue, chest pain and both a personal and a family history of heart disease, it may be that type B scores relate to exhaustion and emotional depletion, which have elsewhere been found to be harbingers of poor outcome in heart disease.[16]

Role of other risk factors: There were some differences in discriminating variables depending on the presence or absence of the surgically treated cohort. For the medically treated group alone, the presence of electrocardiographic Q waves, age, stress and low level

TABLE III

Summary Discriminant Analysis of Variables Related to Morbidity*

In medically treated patients (n = 10)	
Severity of angina	
History of myocardial infarction	
Family history of heart disease	
Electrocardiographic Q waves	
Age	
Stress	
Absence of type A behavior	
Low anger acknowledgment	
Fatigue	
Canonical correlation	0.52
Significance	$p < 0.0001$
Total predictive accuracy	83%
In total sample (n = 189)	
Severity of angina	
History of myocardial infarction	
Family history of heart disease	
Fatigue	
Absence of type A behavior	
Depression	
Low cholesterol	
Canonical correlation	0.42
Significance	$p < 0.00005$
Total predictive accuracy	78%

* All variables are listed in order of importance. Discriminating variables common to both analyses are printed in italics.

of acknowledgment of anger were discriminating variables. For the group as a whole, depression and low serum cholesterol were discriminating variables. The inverse relation between cholesterol level and morbidity may be a chance finding or may reflect the relative absence of beneficial HDL cholesterol.

The number of diseased vessels was not a discriminating variable, a surprising finding in view of much evidence to the contrary.[17–19] This finding is possibly explained by the strong association in our patients between surgical treatment and multiple vessel disease ($r = 0.37$, $p < 0.001$). If these patients had not undergone surgery, they might have accumulated more morbid events.

Finally, there was the impact of the shadow of the past; the family history of heart disease remained relevant to prognosis in this cohort of men already afflicted with heart disease. Something related to such a genetic or personal background persists in conveying substantial risk to the individual patient above and beyond the other risk factors.

Implications: Our approach has been to utilize the maximal amount of data derived from very different theories of risk. When scrutinized closely, many commonly used variables are so highly interrelated that they fail to aid in estimating patients' prognoses after other variables have been considered. By using a combination of clinical findings, laboratory findings, psychosocial assessment and data on epidemiologic exposure to risk factors, one can obtain sufficient information to estimate the prognosis of patients with coronary artery disease.

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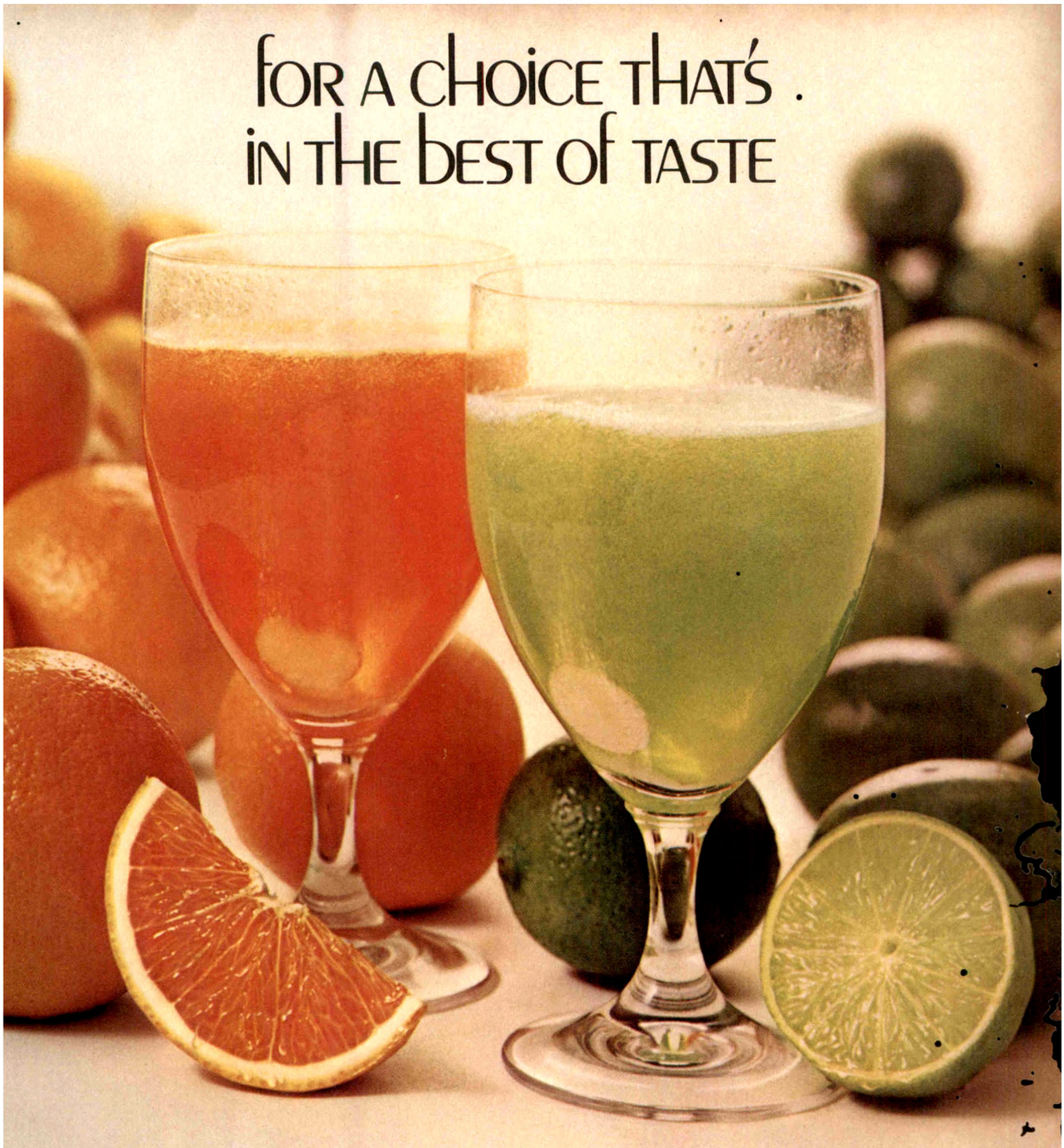

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Update on Oral Anticoagulation

TREATING MYOCARDIAL INFARCTION AND REDUCING THE THREAT OF THROMBOEMBOLISM

Each year in this country approximately one million people suffer acute myocardial infarctions. Rapid emergency treatment in coronary care units has been credited with reducing by up to one third the mortality among patients hospitalized with acute attacks.[1]

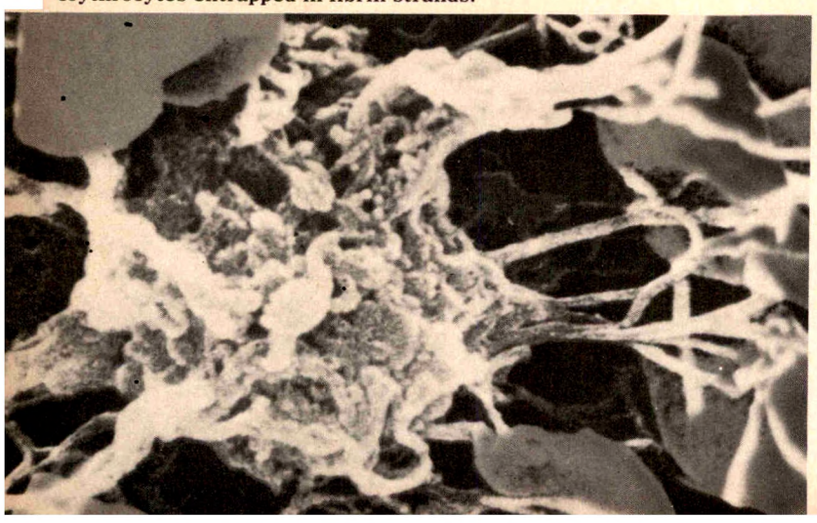
Thrombosis—incidence in myocardial infarction Following the damage to the heart itself, thromboembolism is perhaps the most serious sequel to myocardial infarction.

A study has demonstrated that there is a 39% incidence of calf vein thrombosis during the acute phase of myocardial infarction.[1]

Speed saves lives It has been reported that more than half the thrombi destined to occur in the calf veins form within 72 hours of myocardial infarction, and three-fourths form within the first week. Therefore, a number of investigators have recommended that antithrombotic measures should begin upon admission to the hospital and be effective almost immediately.[2]

Oral anticoagulants have a clinical value It has also been stated that the use of anticoagulants may reduce the frequency of calf vein thrombosis from 22 to 6.5%. The use of anticoagulants is subject to differing opinions regarding improved survival. A number of authorities recommend the use of anticoagulants in *all* patients who have no specific contraindications during the period of hospitalization.[1]

Scanning electron micrograph of 'Red' thrombus, formed by erythrocytes entrapped in fibrin strands.



One team of investigators in M.I. recommends providing full-dose warfarin while the patient is in the hospital and for several days afterward—

if the patient has had prior infarcts or thromboembolism
if the area of infarction is large
if complications (such as CHF or hypotension) require prolonged bed rest.

But, if post myocardial infarction syndrome (Dressler's syndrome) develops, anticoagulants should be discontinued, as pericardial hemorrhage or even cardiac tamponade may develop.[1]

Objectives and benefits of anticoagulation The use of anticoagulants in the acute phase of myocardial infarction has these potential advantages:[2]

prevention of deep vein thrombosis
reduction of embolization from cardiac mural thrombi
prophylaxis against extension of myocardial necrosis or long-term recurrence of infarction
reduction of overall mortality

If anticoagulants can inhibit the formation of deep vein thrombi, then the incidence of pulmonary embolism might be diminished—and pulmonary embolism has been estimated as a threat to life in 5,000 of the 500,000 myocardial infarction patients who are admitted to hospitals in this country each year.[2]

A look at survival One retrospective study of the use of anticoagulants in M.I. evaluated the survival of 1,307 patients from 20 hospitals in a large metropolitan community. The diagnosis of M.I. was based on predefined criteria, which included typical chest pain, serial ECG's, enzyme elevations, and autopsy findings.

Among anticoagulated patients, the adjusted in-hospital case-fatality rate was 18%. For patients who did not receive this treatment, the fatality rate was 31%. For survivors followed for as long as ten years, patients who had been anticoagulated still fared better than those not so treated.[3]

The authors of this study recognize

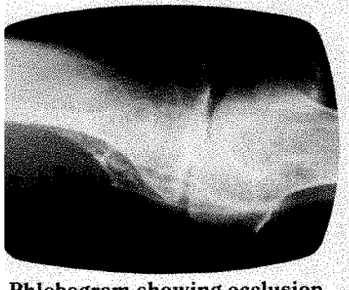
the drawbacks of using retrospective evidence and call for the formation of a multi-center, double-blind, randomized study on the use of anticoagulants in acute myocardial infarction.

Screening the high risk group The risk of DVT (deep vein thrombosis) is particularly great among certain patient groups:

patients with left ventricular failure
patients in shock
patients with arrhythmias
older patients
obese patients
patients with varicose veins
patients with previous myocardial infarction or thromboembolism

Screening techniques Diagnosis of DVT by physical examination may miss a significant number of clinically silent thrombi. There are, however, additional technological tools to help the clinician define more accurately the incidence of deep vein thrombosis. Among these are:

iodine-125 fibrinogen scanning—radioactively tagged fibrinogen is incorporated into actively forming thrombi and is detected on external sensors. This method is accurate for popliteal and calf vein thrombi, but not for iliofemoral thrombi.[2]



Phlebogram showing occlusion in deep vein of the upper calf.

venography—radiographic evidence of DVT is seen as a constant filling defect in venous projections, abrupt termination of a column of contrast material at a constant site, nonfilling of the deep veins, and presence of flow in collateral veins.[4]

ultrasound—Doppler ultrasound scanning can provide a fast, convenient, inexpensive reading of deep venous obstruction. This technique is potentially the most versatile and accurate method available. However, it demands considerable operator experience to insure maximal accuracy.[5]

impedance plethysmography—this technique results from the observation that blood volume changes in the calf produced by inflation or deflation of a thigh cuff produce variations in electrical resistance (impedance). Such changes are reduced in patients with thrombosis of the popliteal or more proximal veins.[4]

Patient compliance through education Providing the anticoagulated patient with information about his altered physical state and motivating him to comply with the therapeutic regimen constitute one of the most important aspects of health care.[6]

To determine the best way of imparting necessary information about anticoagulation to patients, a test was devised. One group of patients was given a brochure detailing the need for the medication and the importance of following the doctor's instructions. A second group of patients was given a programmed instruction booklet which was quite comprehensive in its teaching content, which included the action of warfarin, the purpose of prothrombin times, how to figure dosage from tablet strengths, possible complications and steps to take to control them.

When tested for learning and retention, the patients in the programmed instruction group scored significantly higher than the group given brochures only. In an area of medicine that relies so heavily on patient compliance, this report could be important in determining how medical information is communicated to the patient.[6]

The bottom line A postmortem study[7] underlines the importance of thrombosis in myocardial infarction. In this study of 173 patients with recurrent myocardial infarction, coronary occlusion due to thrombosis occurred in 54% of cases. Recent occlusive coronary thrombosis was 4 times less frequent in patients who received adequate anticoagulation (mean prothrombin level was 29 ± 5%).

And as one authority states:

"Rational use of anticoagulant therapy in the setting of acute myocardial infarction may save more than 8,000 lives a year in this country. Full advantage should be taken of this therapeutic opportunity."[2]

For prescribing information on COUMADIN® (crystalline warfarin sodium) tablets, including information relating to side effects and contraindications, please see full prescribing information on the following page.

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TABLETS

DESCRIPTION COUMADIN (crystalline warfarin sodium), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN (crystalline warfarin sodium) usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN (crystalline warfarin sodium) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system; (2)eye; (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts; (2)cerebrovascular hemorrhage; (3)aneurysms—cerebral, dissecting aorta; pericarditis and pericardial effusions; (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN (crystalline warfarin sodium) are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended, taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma, collagen disease; congestive heart failure, diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol, aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; COUMADIN (crystalline warfarin sodium) overdosage, dextran; dextrothyroxine, diazoxide, dietary deficiencies; diuretics†; disulfiram, drugs affecting blood elements, ethacrynic acid; glucagon; hepatotoxic drugs, indomethacin, inhalation anesthetics; mefenamic acid, methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; pyrazolones, phenylbutazone; phenyramidol, phenytoin, prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting, sulindac, thyroid drugs, tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

*Present as crystalline sodium warfarin isopropanol clathrate.

†Increased and decreased prothrombin time responses have been reported.

COUMADIN is an Endo registered U.S. trademark.

EDO-924C Printed in U.S.A. Nov. 1980

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN (crystalline warfarin sodium) underdosage; diet high in vitamin K; diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN (crystalline warfarin sodium) patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction—40 to 60 mg for average acult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X is not accelerated by the administration of a loading dose.

Maintenance—Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy—The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery—The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin—Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe.

It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium, USP). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

Injection manufactured by Lypho-Med, Inc., Chicago, Illinois 60651 for Endo Laboratories, Inc.

6037-16 Revised Jan. 1980

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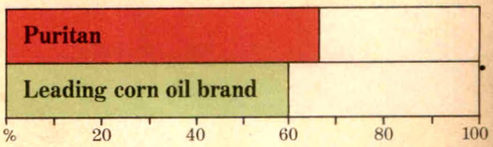
Puritan® Oil–a proven ingredient of cholesterol management

While the etiology of atherosclerosis and coronary heart disease involves many factors..."Cholesterol seems to be the thread running through the web of circumstances culminating in a clinical atherosclerotic event."*
A diet that includes Puritan Oil has been clinically proven effective in reducing serum cholesterol.

Puritan® Oil–superior in polyunsaturates to corn oil

Puritan Oil is made principally from highly polyunsaturated sunflower oil. Puritan provides polyunsaturate levels superior to those of corn oil, the previous standard in a cholesterol-management diet.

A comparison of polyunsaturate levels



Unsurpassed culinary appeal helps encourage patient compliance
Light taste and unsurpassed culinary performance encourage patient compliance in successful long-term dietary management.

*Kannel, W.B.: The role of cholesterol in coronary atherogenesis, Med. Clin. North Am. 58:363-379, 1974.

INTRODUCING STATUS 1000

WITH AN IMAGINATION TO MATCH YOUR OWN

Status 1000, The ECG Monitor That Gives You Programmable Control Over Every Aspect Of The Stress Test.

Quinton's Status 1000 is the first ECG stress test system that lets you use your imagination to modify or reprogram at will the various elements of a stress test.

Not just treadmill protocol, but lead selection, ST sample point, recorder speed, patient name, final report content and length, blood pressure prompting, etc. Everything is in your control like it should be.

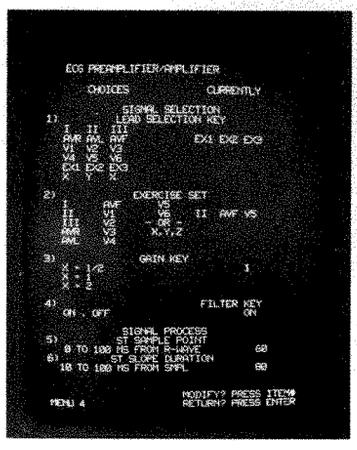
Use your professional imagination to create and program customized test procedures for pediatric, research, post-M.I., rehab., or out-patient situations.

Each physician in your institution can have their own preferred test procedure stored in memory.

With the Status 1000 you and your colleagues can customize test procedures based on the requirements of the patient, not the restrictions of the ECG system.

How The Sophisticated Status 1000 Makes Test Flexibility So Complete And Easy

With The Status 1000, Quinton introduces a new term, the "Stress Test Environment". It consists of 16 test elements. Each element, such as exercise lead set, or final report content, has parameters which you can establish or modify to suit your needs.



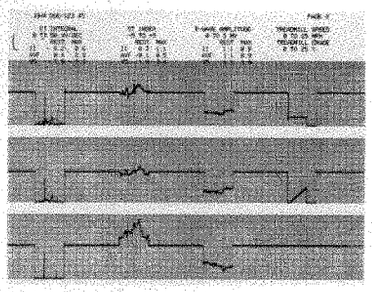
Yet, programming the Status 1000 is as easy as operating a pocket calculator, so special training is not required.

Comprehensive Data, Professionally Presented

In a single glance you see three channels of diagnostic quality ECG, averaged beats (both resting and current), heartrate, computed parameters, trend displays, stage number, stage time and elapsed time.

Plus, any abnormal beat will be instantly highlighted on the screen, then recorded and labeled automatically.

Your control extends to test reports, too. Printouts during the test may include averaged beats, rhythm strips, or full 12-leads. Final reports may include a wide variety of information. And each report is automatically labeled with pertinent data. Good bye work sheet.



Stay Ahead With The Status 1000

Because of the Status 1000's unparalleled flexibility and microprocessor technology its susceptibility to obsolescence is far less than other systems. And that makes it a good investment for you and your institution. Call Quinton toll free at 1-800-426-0538.

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III

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For Short-Term
Inotropic Support in Patients w
Low-Output Cardiac Failure

Selectively Increases
Myocardial Contractility
with Consistent
Hemodynamic Improvements

Dobutrex®
Dobutamine HCl

For I.V. Injection
250 mg* in 20-ml-size vials
* Equivalent to dobutamine

Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250,500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

[081678]

Lilly

Additional information available to the profession on request.

Eli Lilly and Company
Indianapolis, Indiana 46206

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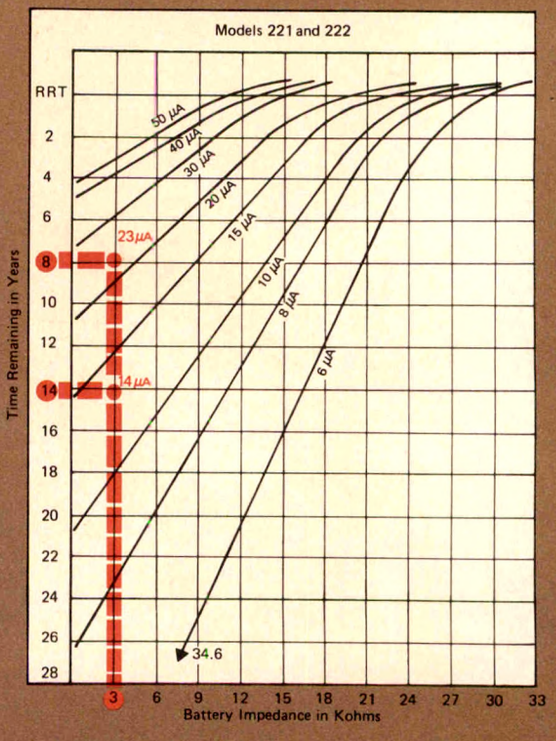
The simplest of these interrogatable pacemakers, the Programalith 'O', is perhaps the most sophisticated of all, in its way.

The Programalith 'O' requires no programming, yet it can be interrogated for all measured data (see chart at right), providing invaluable assistance in long-term patient management.

The Programalith 'O' can tell quite a story: It provides information for calculating the remaining battery capacity of the implanted pacemaker, gives the physician data for assessing possible lead problems – *and* their location – and provides battery impedance and battery current as well.

The story of 'O' – Pacesetter Systems style – may be one of the most important stories of the year, for physicians, for patients, and for the pacer industry itself.



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ing. Simplified.

The exclusive programming head on the Pacesetter Prog programming console enables the physician to interrogate the Pacesetter 'O' pacer in all parameters. Another reason we're called Pace*setter*.

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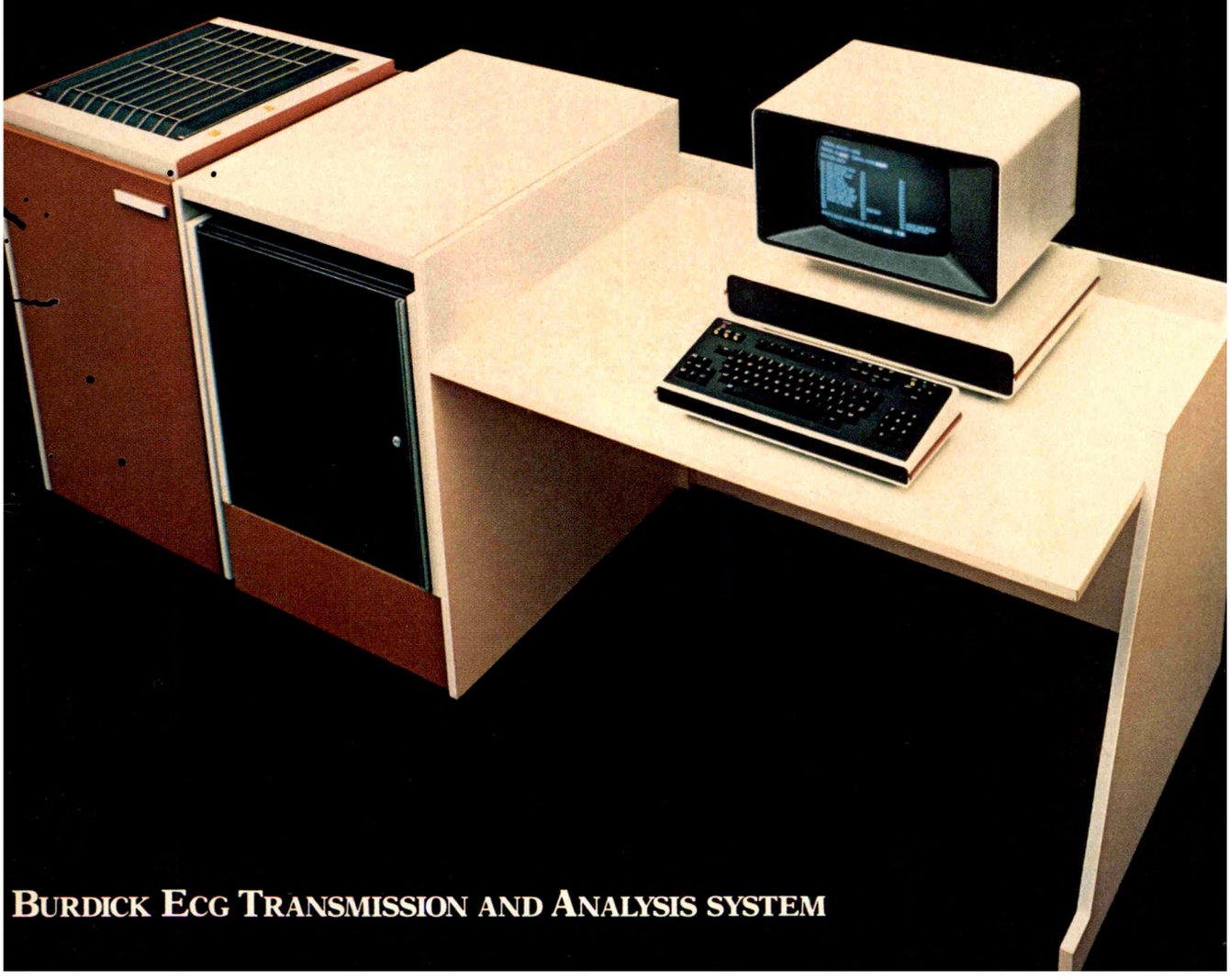
BURDICK INTRODUCES

BETA



BURDICK ECG TRANSMISSION AND ANALYSIS SYSTEM

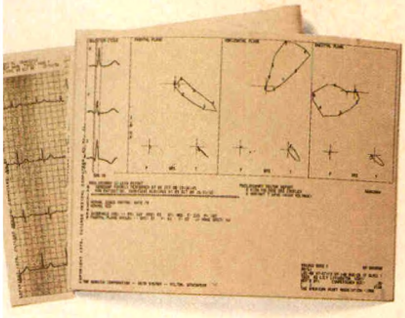
IT'S FIVE FULL STEPS AHEAD OF ANY OTHER COMPUTERIZED ECG SYSTEM.

Computerized ECG technology has just made a remarkable advance. Burdick has taken its leadership experience in the field of electrocardiography and combined it with some of the most sophisticated medical computer technology available today.

The result is the Burdick BETA™, a computerized ECG system that combines today's most comprehensive ECG analysis with a complete backup for acquisition, storage and retrieval that is both efficient and cost-effective. In fact, BETA is ahead of any other computerized ECG system in five important ways.

1. THE ONLY SYSTEM WITH SCALAR/VECTOR ANALYSIS

The combination of 12-lead Scalar (ECG) data and 3-dimensional Vector (VCG) data in a single, complete analysis is the Burdick breakthrough that assures a more complete, accurate diagnosis. BETA is the



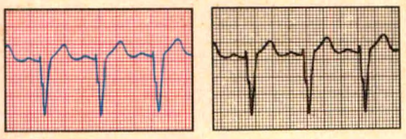
only computerized ECG system that combines simultaneous Scalar/Vector data with the technology of automated computer analysis, providing patient diagnosis of enhanced sensitivity and specificity.

2. THE ONLY SYSTEM THAT STORES AND RETRIEVES OPTICALLY AND NUMERICALLY CORRECT ECGS

Until now, computerized ECG systems have sacrificed the quality of their retrieved ECGs to achieve greater data storage.

BETA is the first system to offer cost-effective, unlimited, on-line mass storage of ECG/VCGs, with fast retrieval by means of a unique master indexing system using patient or hospital coding.

While some systems indiscriminately compress at ratios of as much as 15 to 1, BETA virtually eliminates data compression. The result is that users are able to retrieve cardiograms that are optically and numerically correct, with no degradation of original data. That, of course, makes possible accurate re-analysis.



Original ECG

BETA'S non-compressed data

3. THE ONLY SYSTEM IN WHICH ALL SATELLITES HAVE TOTAL ACCESS TO HOST HOSPITAL CAPABILITIES

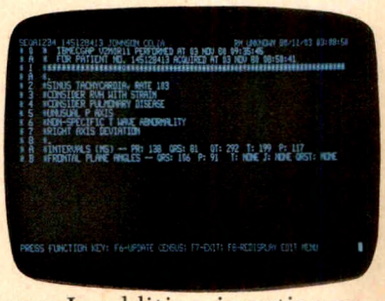
In a BETA installation, satellite hospitals are more than just appendages. They share fully in all the capabilities enjoyed by the host hospital, such as security, mass storage, Scalar/Vector analysis, free-form editing, and other options, including direct communication with each satellite hospital medical information system.

That way the satellites have all the advantages of their own BETA system without the capital expense. Conversely, host hospitals can offer comprehensive, yet cost-effective service to prospective satellite hospitals.

4. THE ONLY STORAGE SYSTEM DESIGNED FOR FREE-FORM EDITING

All editing of computer-generated analysis on the BETA video display terminal is done in plain language. The physician and staff can enter their changes or additions in the words they choose, any place in the text.

It is not necessary to memorize codes, reducing possibility of



error. In addition, insertion or deletion of words or sentences can be made anywhere in the text. This eliminates footnote form editing.

5. THE ONLY FULL-RANGE SYSTEM WITH COMPLETE MODULARITY FOR FUTURE NEEDS

You can start with an economical base system. And as your needs develop, you can add Vector analysis, additional storage capacity and other functions. There is no need to replace original equipment to get increased system capability.

And since BETA stores completely re-analyzable cardiograms, your on-line data base always remains intact as you build the system.

PLUS . . . MULTI-LEVEL PATIENT DATA SECURITY

With the Burdick BETA System you have available several levels of patient data security that virtually eliminate the possibility of unauthorized access and/or alterations to stored data. The system assures the hospital of complete integrity and privacy of patient information

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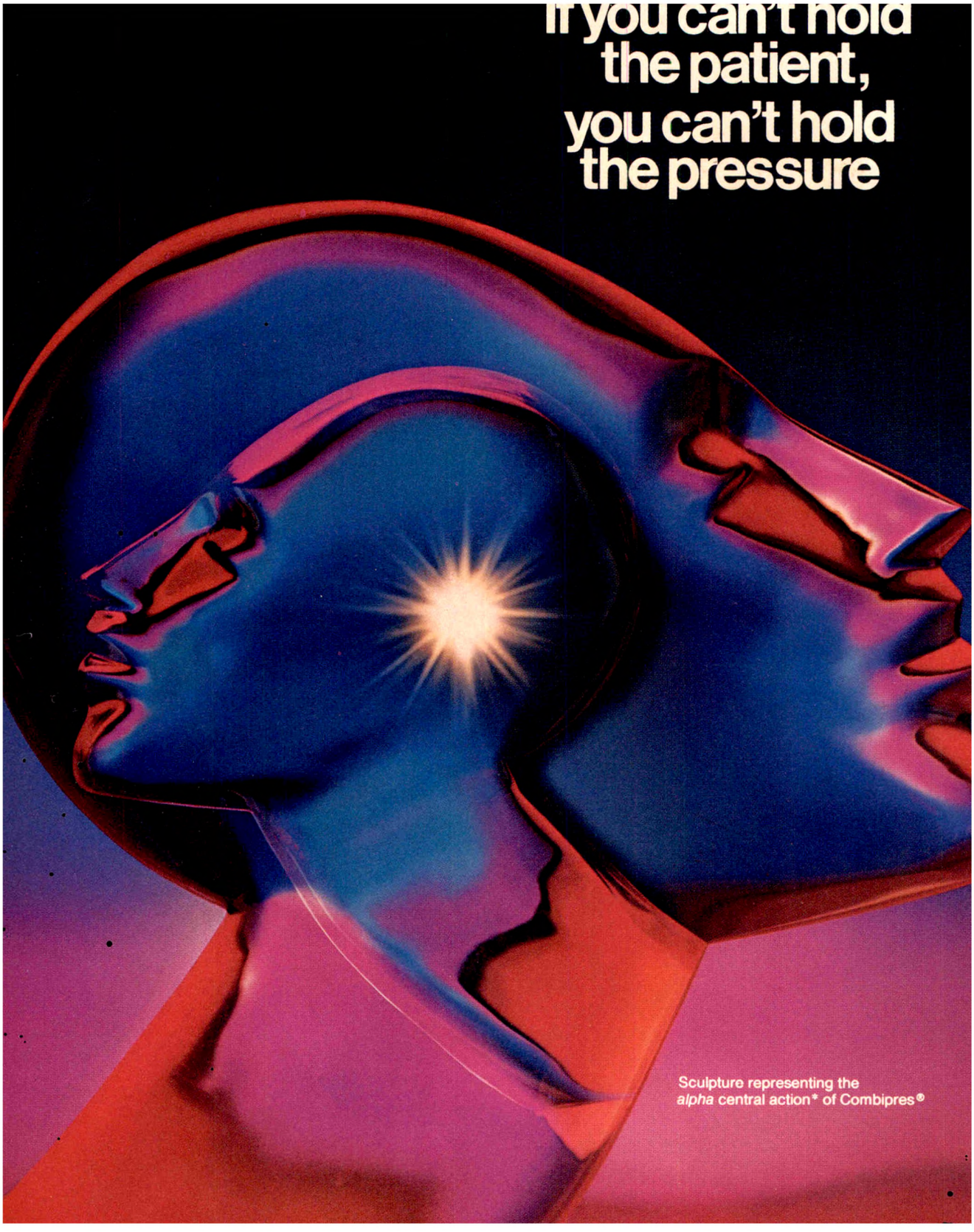
A concern for cardiac care.


If you can't hold
the patient,
you can't hold
the pressure
Sculpture representing the
alpha central action* of Combipres®

Alpha... hold the pressure

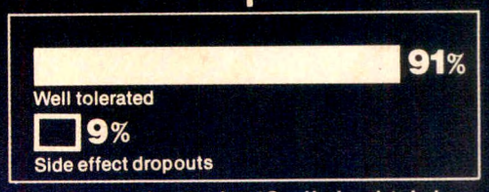
- central control of blood pressure*
- low incidence of impotence, depression, orthostatic hypotension**
- most common side effects are dry mouth, drowsiness and sedation, which generally tend to diminish with time. As with other agents containing diuretics, hypokalemia, hyperuricemia, and hyperglycemia may occur.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

**Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.

plus... hold the patient

91% compliance†



†Of 484 patients in 16 clinical trials, only 9% definitely or probably dropped out due to side effects.[1]

[1] Data on file, Boehringer Ingelheim Ltd.

Please see brief summary on last page for warnings, precautions, and adverse reactions.

Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

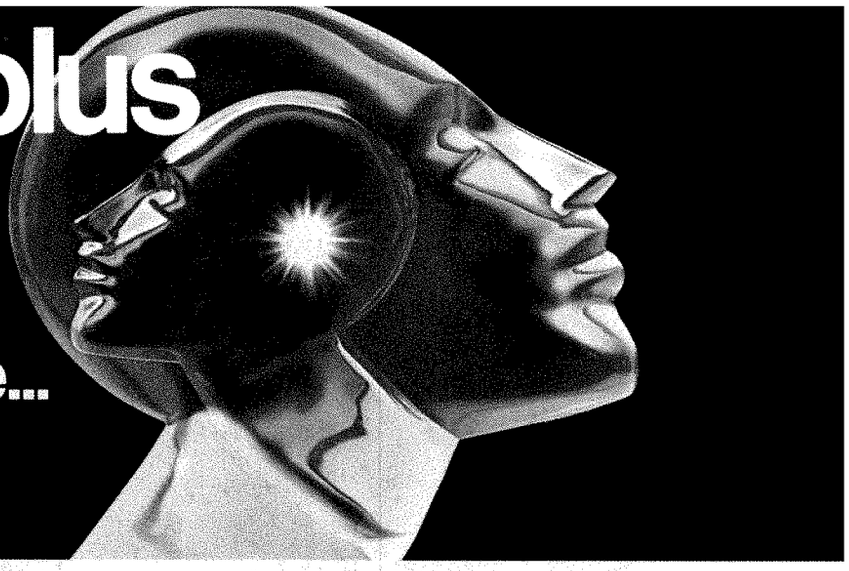
Combipres®

Each tablet contains: Catapres® (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

.1 and .2

Hypertension

Alpha...plus



hold the pressure...
hold the patient...

Combipres® .1 and .2

Each tablet contains: Catapres® (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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Lung Biopsy With Frozen Section as a Diagnostic Aid in Patients With Congenital Heart Defects

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In eight patients with congenital heart defects and equivocal preoperative hemodynamic data, lung biopsy with frozen section was performed and quantitative morphometric analysis carried out to help select a palliative or corrective surgical procedure. During catheterization it had been possible in only six of the eight patients to enter the pulmonary artery and obtain pressure measurements; four patients had moderate to severe elevation of pulmonary vascular resistance whereas the other two had only mild elevation of pulmonary arterial pressure, but they were being considered for a Fontan procedure.

The lung biopsy tissue was taken inflated and fixed inflated in hot glutaraldehyde. From cryostat sections arterial concentration was assessed relative to alveolar concentration, and the degree of arterial muscularity was assessed by wall thickness and extension of muscle; the more advanced Heath-Edwards arterial changes were also evaluated. On the basis of the morphologic assessment, six of the eight patients underwent corrective surgery and two underwent a palliative procedure. Postoperative hemodynamic data available in four of the patients who underwent corrective surgery revealed either a significant reduction in pulmonary vascular resistance or return to a normal level of pulmonary arterial pressure, whereas no change has occurred in the one patient studied who underwent a palliative procedure. Assessment of pulmonary arterial development and structure on lung biopsy with frozen section proved helpful in deciding between a palliative and corrective surgical procedure.

Patients with congenital heart defects complicated by pulmonary vascular changes and elevated pulmonary vascular resistance may not be suitable candidates for corrective surgery.[1–5] Whereas severe and irreversible elevation in pulmonary vascular resistance precludes a favorable hemodynamic result after surgical closure of a ventricular septal defect,[1,2] even mild elevation will result in right heart failure after a Fontan-type procedure for tricuspid atresia and related lesions.[5]

The level of pulmonary vascular resistance determined at preoperative cardiac catheterization reflects the behavior of the pulmonary circulation at one time only and may not be representative. In patients with either severe subpulmonary stenosis or atresia and a surgically created systemic to pulmonary arterial shunt, it may be very difficult to enter the pulmonary artery and to obtain pressure measurements; in these cases, the catheter itself may compromise pulmonary blood flow and pulmonary arterial pressure may be falsely decreased. In some patients, because of the size or the configuration of the systemic to pulmonary arterial anastomosis, it may not be possible or prudent to enter the pulmonary artery at all. Moreover, direct assessment of pulmonary arterial pressure through pulmonary venous wedge pressure measurement has not proved reliable.[6]

It is therefore important to have an alternative way to assess pulmonary circulation. Through morphometric analysis of lung biopsy tissue, we have determined the type and severity of abnormalities of structure

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and growth of the peripheral pulmonary arteries that reflect increased pulmonary blood flow, pressure or resistance.[7] We have now applied these quantitative techniques of analysis to examine lung biopsy tissue prepared by frozen section at the time of operation. In patients whose hemodynamic data were equivocal, unreliable or could not be obtained, this technique has been useful in deciding whether to perform a palliative or a corrective operation.

Methods

Study Patients (Table I)

In eight patients with congenital heart defects, whose ages ranged from 1 to 24 years, it was not certain from the hemodynamic and angiographic data whether a corrective or palliative surgical procedure was indicated. Two patients (Cases 1 and 2) had d-transposition of the great arteries with associated ventricular septal defect; two (Cases 3 and 4), complete common atrioventricular canal; three (Cases 5 to 7), tricuspid atresia (all with severe subpulmonary stenosis and one or more previously surgically created systemic to pulmonary arterial shunts); and one (Case 8), tetralogy of Fallot with pulmonary atresia and large aortopulmonary collateral vessels.

Cardiac catheterization findings: In six of the eight patients, the pulmonary artery was entered and pressure measured; in the other two this was not technically possible. In three of the six patients whose pulmonary arterial pressure was measured, pulmonary vascular resistance was elevated (8 to 14 U/m^2). In one of these patients (Case 3), the pulmonary vascular bed responded to priscoline (1 mg/kg given intravenously) with a decrease in pulmonary vascular resistance of 6 U/m^2, but in another patient (Case 2), neither priscoline nor breathing 100 percent oxygen for 15 minutes caused any change. The third patient with elevated pulmonary vascular resistance (Case 4) was extremely restless during cardiac catheterization and was not at steady state long enough to be tested satisfactorily with oxygen or priscoline. In a fourth patient (Case 1), pulmonary vascular resistance was only mildly elevated, but this patient had d-transposition of the great arteries complicated by both a ventricular septal defect and a patent ductus arteriosus and was considered at high risk for the development of pulmonary vascular disease.[8,9] Because it is particularly difficult to calculate reliably the level of pulmonary vascular resistance in d-transposition of the great arteries, it was believed this might be a misleading result.[10,11]

Two other patients had only mildly elevated pulmonary arterial pressure, but both were being considered for a Fontan procedure.[5] Because the Fontan procedure involves either a conduit or a direct anastomosis between the right atrium and the pulmonary artery, it must be ensured that the level of pulmonary arterial pressure and resistance be normal postoperatively. In one of these patients (Case 6), the level of pulmonary arterial pressure had been normal at cardiac

TABLE I

Hemodynamic and Morphologic Lung Biopsy Data Analyzed From a Frozen Section in Eight Patients

Case	Diagnosis	Age (yr)	Preop Hemodynamic Data P_{pa} (mm Hg)	Rp (U/m^2)	Rp/Rs	Morphometric Grade (A, B, C)	Heath Edwards Grade (I–VI)	Surgery	Postop Hemodynamic Data P_{pa} (mm Hg)	Rp (U/m^2)	Rp/Rs Ratio
1	dTGA + VSD + PDA	1	$\overline{55}$	3.0	0.4	B	I	Corrective: Mustard procedure VSD closure, PDA ligation	$\overline{33}$‡	2.1	0.2
2	dTGA + VSD	3	$\overline{52}$	9–14*	0.5–0.7	C	III (late)	Palliative: Mustard procedure, VSD left open	$\overline{63}$	6–7	0.4
3	A-V canal	3	$\overline{66}$	9.3 3.4 (priscoline)	0.5	C	I	Corrective	$\overline{33}$	6	0.2
4	A-V canal	4	$\overline{43}$	7.9	0.3	B	I	Corrective	—	—	—
5	Tricuspid atresia; S/P Waterston shunt.	7	$\overline{28}$† 14	3.0† 1.5	0.1 0.1	A	0	Corrective: Fontan procedure, closure of Waterston anastomosis	$\overline{7}$	1	0.1
6	Tricuspid atresia; S/P right Blalock-Taussig shunt	7	$\overline{21}$	2.2	0.2	0	0	Corrective: Fontan procedure, closure of right Blalock-Taussig shunt	$\overline{8}$	1	0.1
7	Tricuspid atresia; S/P Waterston shunt; S/P left Blalock-Taussig shunt	9	NE	—	—	C	III–IV	Palliative: Central shunt	—	—	—
8	Tetralogy of Fallot + pulmonary atresia	24	NE	—	—	0	0	Corrective: VSD closure + valved conduit from RV to main PA	—	—	—

* No significant change with 100 percent oxygen or priscoline. † Two measurements, one close to shunt orifice, one very distal. ‡Pulmonary arterial wedge pressure = 21 mm Hg.

A-V = atrioventricular; dTGA = d-transposition of the great arteries; NE = not entered; PA = pulmonary artery; PDA = patent ductus arteriosus; Postop = postoperative; P_{pa} = mean pulmonary arterial pressure; Preop = preoperative; Rp = pulmonary vascular resistance; Rs = systemic vascular resistance; Rp/Rs = ratio of pulmonary to systemic vascular resistance. RV = right ventricle; S/P = status postoperative; VSD = ventricular septal defect.

catheterization 2 years before operation, but intraoperatively the pulmonary arterial pressure was elevated. It was uncertain whether this elevation was the effect of anesthesia or truly reflected the state of the pulmonary vascular bed. In the other patient (Case 5), pulmonary arterial pressure varied with the position of the catheter; when the measurement was taken close to the orifice of the systemic to pulmonary arterial shunt the value was high, whereas when it was recorded more distally, it was normal.

The pulmonary artery could not be entered and pressure could not be recorded in two patients. One of these patients had tricuspid atresia and was being considered for a Fontan procedure; two different systemic to pulmonary arterial shunts had previously been produced surgically, but it was not possible to enter either shunt. The other patient had tetralogy of Fallot with pulmonary atresia and large tortuous aorto-pulmonary collateral vessels; because no obvious stenoses were identified angiographically, severe pulmonary vascular changes in the lung were suspected.[12]

Method of Lung Biopsy

The lung biopsy was performed after the chest was opened; in all patients tissue was taken from the medial aspect of the right upper lobe, but in one patient tissue was also taken from the left upper lobe. First, the lungs were fully inflated at a pressure ranging between 16 and 32 cm of water depending on the weight of the patient. Two "C" clamps were placed on the lung and a piece of tissue 1 by 2 by 0.5 cm was isolated (Fig. 1). The tissue between the clamps was incised and the distal clamp containing the inflated tissue was submerged for 10 minutes in warmed (40° C) 2.5 percent glutaraldehyde solution. The glutaraldehyde was made up in 0.2 molar cacodylate buffer; the final pH was 7.4 and osmolarity 434 mosmol/liter. The clamp was then released and a piece of tissue 1 by 0.2 by 0.5 cm was cut perpendicular to the pleural surface and mounted for cryostat sections. Six sections, taken at least five sections apart, were flame-fixed to albuminized slides to which elastic Van Gieson stain was applied. This stain is most useful for measuring the thickness of the arterial muscular coat and for assessing the degree of extension of muscle into small peripheral arteries. The remaining tissue was kept submerged in glutaraldehyde for an additional 2 hours of fixation, after which routine paraffin embedding was carried out. Twenty-four hours later, tissue sections, stained with elastic van Gieson in addition to hematoxylin-eosin and Gomori's trichrome stain, were available for comparison with the frozen sections.

Analysis of Lung Biopsy Tissue

Frozen section morphometric analysis: Morphometric analysis of all the arteries of all the fields was carried out in each of the six frozen sections. Although the same larger arteries could be identified in all sections, a few additional smaller arteries were generally found in each consecutive section. It was usually possible to identify 10 to 15 arteries in 5 to 10 fields (power × 20) in each section.

The following features of peripheral arterial structure were studied: The external diameter of an artery was measured with a calibrated eyepiece micrometer between the external elastic laminas across the shorter axis of the vessel. Wall thickness was measured across the shorter axis from external to internal elastic lamina because this has been shown to represent the true wall thickness even in vessels cut obliquely.[13] Percent wall thickness was then calculated:

$$\frac{2 \times \text{Wall thickness}}{\text{External diameter}} \times 100 = \% \text{ Wall thickness}$$

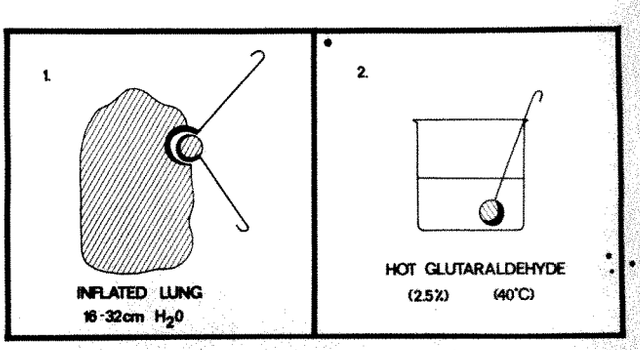

FIGURE 1. Diagrammatic representation of (1) an inflated lung with 2 C clamps on the upper medial aspect, and (2) the C clamp containing the biopsy tissue submerged in hot glutaraldehyde.

Arteries were grouped according to size and the percent wall thickness calculated for each size range. Where a small artery accompanied a small airway, it was characterized or landmarked by reference to the type of airway it accompanied: The levels recognized were preacinar, terminal bronchiolus, respiratory bronchiolus, alveolar duct and alveolar wall. In this manner, the structure of the artery related to airway level offers one way of assessing extension of muscle along the arterial pathway. Thus, increased arterial muscularity is apparent from an increased wall thickness related to the size of an artery or to the presence of muscle in arteries that are either smaller or in a more peripheral position along the arterial pathway than is normal. The number of arteries larger than 10 μm and alveoli were counted in each section and expressed as a ratio. This made allowance for any difference in the degree of inflation in the various biopsy tissues. The value obtained for each morphometric feature was compared with the previously established age-related normal value[7,13,14] (Table II).

The biopsy tissue was then graded A, B or C according to the severity of the morphologic changes by a system previously described[7] (Fig. 2). In this system, each new grade requires that all the features of the previous grade be present as well. On the basis of the results of our previous study,[7] we are able, from the grade given to a lung biopsy specimen, to predict whether the level of pulmonary arterial pressure is in the normal range or elevated, or whether the pulmonary vascular resistance is elevated and, in part, the degree of that elevation (Fig. 2).

TABLE II

Normal Morphometric Values on Lung Biopsy

Age	Alveolar Wall Muscular Arteries* (%)	Percent Wall Thickness of Muscular Arteries >50 μ External Diameter†* (%)	Arteries per 100 Alveoli‡
Newborn	0	20	5
4 mo	0	10	5
2 yr	0	10	8
6 yr	31	10	10
Adult	50	10	10

* Upper limit of normal range. † 2 × wall thickness/external diameter × 100. ‡ Lower limits of normal range.

	MORPHOLOGY	PHYSIOLOGY
A.	ABNORMAL EXTENSION OF MUSCLE	↑ PULMONARY BLOOD FLOW
B.	INCREASED WALL THICKNESS if > 1.5 x nl, often if > 2 x nl, always	↑ PULMONARY ARTERY PRESSURE
C.	REDUCED ARTERY NUMBER (usually associated with reduced artery size)	↑ PULMONARY VASCULAR RESISTANCE (≥ 3.5 u/M^2)

FIGURE 2. Morphometric grades of pulmonary vascular disease as they relate to physiology. When the increased wall thickness is greater than twice normal (nl), the designation "late" grade B is given. ↑ = increased.

The biopsy tissue was also analyzed for the more severe structural changes described by Heath and Edwards[15] *and graded accordingly.* Changes of late grade III and grade IV, occlusion and dilatation, respectively, have been shown to be associated with severe and irreversible elevation in the level of pulmonary vascular resistance.[16] The report of the lung biopsy analysis was conveyed to the operating surgeon within 30 minutes from the time the tissue was first obtained.

Analysis of paraffin-embedded sections: It was possible to analyze the paraffin-embedded sections available 24 hours later, in more detail than the frozen sections. Because the former were better fixed and easier to cut, there was less distortion of the tissue. In some cases, this analysis allowed for as much as a two-fold increase in the number of arteries satisfactory for counting and measuring. Also, because the alveolar architecture was better preserved, assessing the concentration of arteries relative to alveoli could be done with greater confidence. The degree of extension of muscle into peripheral arteries was evaluated as described for the frozen section. Because more arteries were measured and, because time was not a factor it was also possible after analysis of the paraffin-embedded sections to calculate a mean and standard error of percent wall thickness for arteries at different airway levels (that is, respiratory bronchiolus, terminal bronchiolus) and for arteries in different diameter ranges (that is, 50, 50 to 99, 100 to 149 and 150 to 199 μ).

Statistical analysis: Findings in the frozen and standard microscopic sections, with respect to the degree of peripheral extension of muscle, the medial wall thickness of the normally muscular arteries and arterial concentration, were compared with the paired *t* tests; a probability (p) value greater than 0.05 was judged to indicate a significant difference

Postoperative Hemodynamic Assessment

In five of the eight patients, postoperative hemodynamic measurements of pulmonary arterial pressure and resistance were also available. In three, complete cardiac catheterization with measurement of oxygen consumption was carried out 6 months to 1 year after operation; the other two patients underwent intracardiac monitoring of pulmonary arterial pressure in the immediate postoperative period and pulmonary vascular resistance was calculated using pulmonary blood flow assessed with the thermodilution technique.

Results

Comparison of frozen and final section (Table I): Analysis of the pulmonary vascular changes revealed similar findings on both the frozen section of the lung biopsy specimen and the paraffin-embedded section (Fig. 3 to 6). This was true especially for the degree of abnormal extension of muscle into small peripheral arteries and for the percent wall thickness of the normally muscular arteries. The concentration of small peripheral arteries was judged to be either the same or somewhat increased in the frozen than in the final paraffin-embedded section. However, the difference was not great and only altered the morphometric grade in one patient (Case 3). Also, knowledge of the value obtained from the final section would not have changed the intraoperative decision to perform corrective surgery. Assessment of the more advanced structural changes of Heath and Edwards revealed similar findings in the frozen and paraffin-embedded sections.

Lung biopsy analysis and prognosis: Patient 2 with d-transposition of the great arteries, a ventricular septal

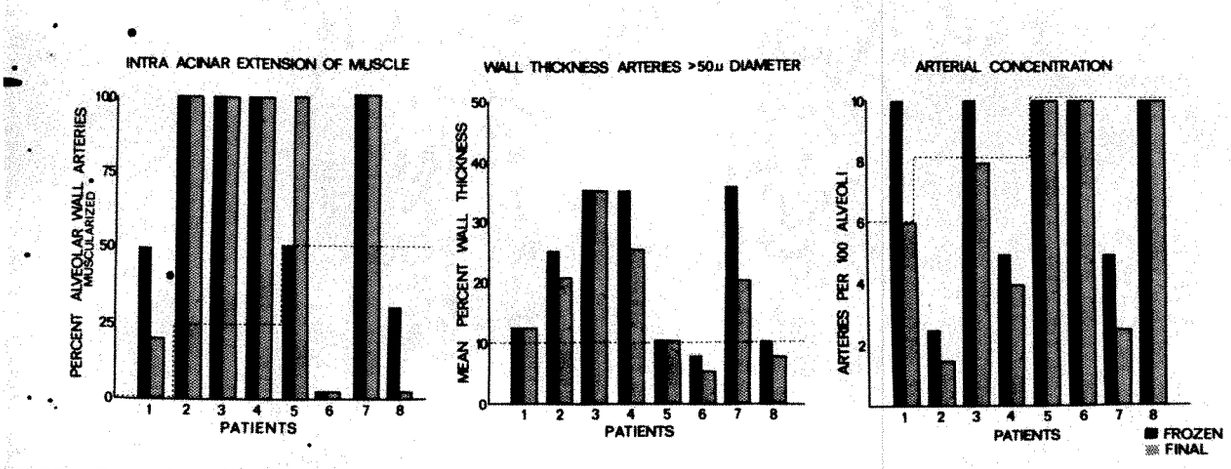

FIGURE 3. Comparison of the quantitative morphometric evaluation by frozen section (**solid bars**) and by paraffin-embedded section (**dotted bars**) of intraacinar extension of muscle, percent wall thickness of normally muscular arteries and arterial concentration expressed as arteries per 100 alveoli. The **top of each bar** represents the upper limit if a range of values was obtained, for example, for percent wall thickness. The **horizontal dotted line** represents the upper limit of normal range for each feature related to the age of the patient it crosses.

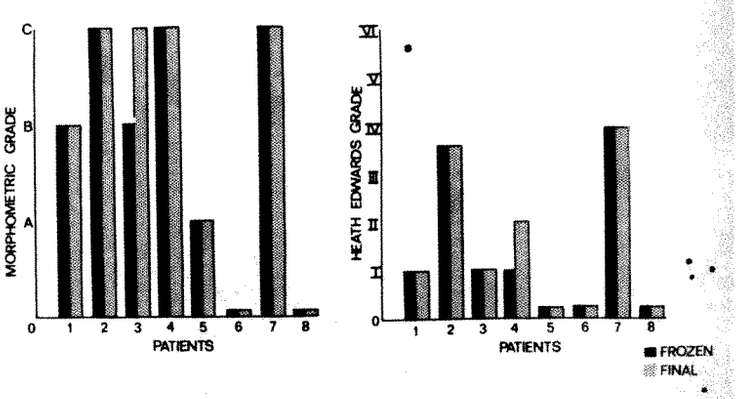

FIGURE 4. Comparison of analysis of frozen (**solid bar**) and paraffin-embedded (**dotted bar**) sections with respect to the morphometric and Heath-Edwards grades given to each patient.

defect and fixed elevation in pulmonary vascular resistance had severe structural changes in the lung biopsy tissue—that is, morphometric grade C, including a severe reduction in arterial concentration as well as Heath-Edwards late grade III changes. After a palliative Mustard procedure was performed,[17] this patient had dramatic improvement in her symptoms; but on follow-up cardiac catheterization 6 months later, the pulmonary vascular resistance was still very high and did not respond to breathing of 100 percent oxygen. Two other patients (Cases 3 and 4), both with common atrioventricular canal and elevated pulmonary vascular resistance, also had grade C morphometric changes but a less severe reduction in the number of arteries than that observed in Patient 2, and none of the severe structural changes of Heath-Edwards. Both underwent complete correction of their defect and had an uncomplicated postoperative course. Only one of these patients (Case 3) has been restudied hemodynamically and in the immediate postoperative period. The pulmonary arterial pressure had decreased to half systemic levels and the pulmonary vascular resistance was significantly decreased. The patient (Case 1) with d-transposition of the great arteries, pulmonary arterial pressure at systemic levels and only mild elevation in pulmonary vascular resistance had grade B changes on lung biopsy. Complete repair was carried out and he had an uneventful postoperative course. Six months later cardiac catheterization was repeated because pulmonary venous obstruction was suspected. His pulmonary arterial

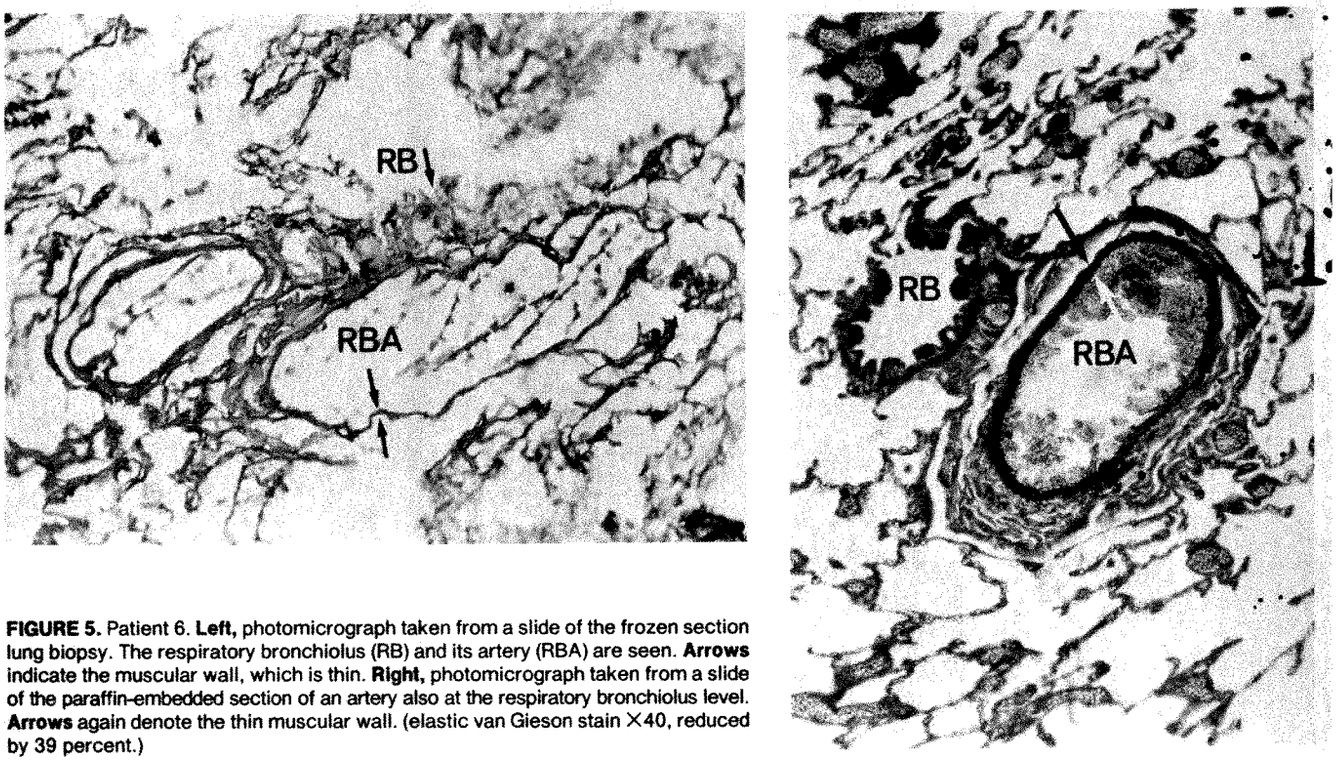

FIGURE 5. Patient 6. **Left,** photomicrograph taken from a slide of the frozen section lung biopsy. The respiratory bronchiolus (RB) and its artery (RBA) are seen. **Arrows** indicate the muscular wall, which is thin. **Right,** photomicrograph taken from a slide of the paraffin-embedded section of an artery also at the respiratory bronchiolus level. **Arrows** again denote the thin muscular wall. (elastic van Gieson stain ×40, reduced by 39 percent.)

pressure had decreased to less than half systemic level in spite of pulmonary venous obstruction, with a mean pulmonary arterial wedge pressure of 21 mm Hg. A further corrective procedure was performed and he awaits follow-up catheterization.

In spite of the large and tortuous aortopulmonary collateral vessels in the patient with tetralogy of Fallot and pulmonary atresia (Case 8), analysis of his lung biopsy tissue showed an essentially normal pulmonary vascular bed. Hence, stenoses of the collateral vessels were probably present although they were not obvious in the preoperative cineangiogram. A complete repair was performed in this patient with no untoward sequelae. Of the three remaining patients who had tricuspid atresia and were being considered for a Fontan procedure, one (Case 5) had only minimal pulmonary vascular changes of abnormal peripheral extension of muscle and another (Case 6) an essentially normal pulmonary vascular bed. In both of these patients, the proposed surgery was performed and in the postoperative period both had reduced levels of pulmonary arterial pressure (Fig. 5 and 7). The third patient (Case 7) had severe structural changes in the right lung with morphometric grade C and Heath-Edwards grade III to IV changes. The left lung biopsy tissue was small and, perhaps also because of the nature of the disease, included only four arteries. One of these vessels also had severe intimal hyperplasia. A Gortex central shunt was placed and the patient did well in the immediate postoperative period but later became progressively more cyanotic.

Discussion

Interpretation of preoperative hemodynamic data: Preoperative hemodynamic data as a basis for predicting postoperative outcome are sometimes very unsatisfactory. In some patients the sedative medication may decrease the level of pulmonary arterial pressure,

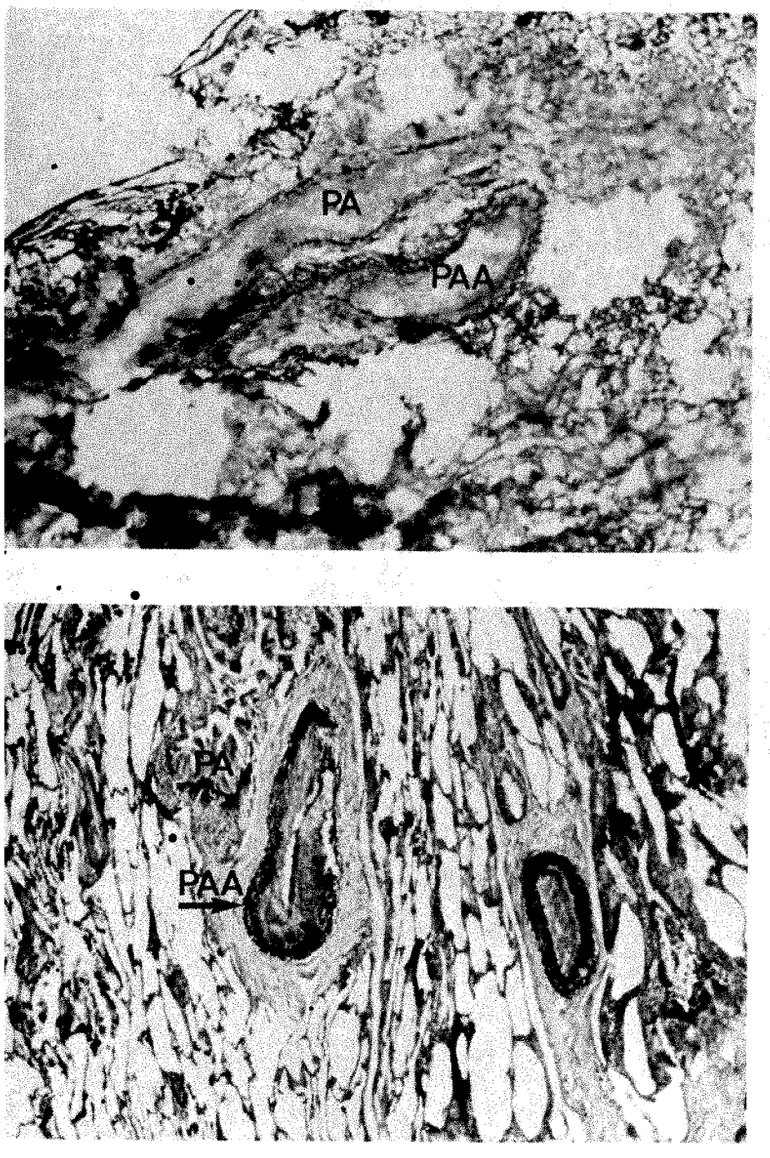

FIGURE 6. Patient 7. **Top,** photomicrograph taken from a slide of the frozen section lung biopsy. The preacinar airway (PA) and its artery (PAA) are seen, the latter with extensive intimal hyperplasia, disruption of the elastic laminae of the media, and dilatation. **Bottom,** a similar level vessel with similar features is seen on a photomicrograph taken from the slide of the paraffin-embedded section. (elastic van Gieson stain ×100, reduced by 39 percent.)

whereas in other patients, alveolar hypoxia, secondary either to upper airway obstruction or to pulmonary edema, may increase it.[18] Testing the reactivity of the pulmonary vascular bed to 100 percent oxygen can usually, but not always, detect the latter.

When the level of pulmonary arterial saturation is very high, as is characteristic in patients with d-transposition of the great arteries, the pulmonary blood flow is usually overestimated[11] and thus the level of pulmonary vascular resistance underestimated. In these patients, the contribution of the bronchial collateral circulation is difficult to assess and so the problem is compounded.

It is hazardous to place too much confidence in a measurement of reduced pulmonary arterial pressure when pulmonary blood flow is also decreased.[19] Mean pulmonary venous wedge pressures have been shown to correlate poorly with mean pulmonary arterial pressures[6] although agreement seems to be better in the lower ranges of pressure.

Morphology as an index of pulmonary vascular disease: Evaluating the morphologic state of the pulmonary vascular bed in lung biopsy tissue to assess the severity of pulmonary vascular disease is not new, but previous studies depended entirely on the Heath-Edwards grading of pulmonary vascular changes, which is helpful but has drawbacks. The more advanced structural changes (grade IV and higher) are uncommon in the first 2 years of life,[20–22] even in the presence of marked elevation of pulmonary vascular resistance. Also, the severe changes are not evenly distributed throughout the lung parenchyma, making it unreliable to assess only a small piece of biopsy tissue.[15] The system of morphometric analysis used here adds additional information at any age. It includes assessment of the earlier changes of abnormal growth and development of the small peripheral arteries that can be detected from the first days of life.[23] Moreover, these changes have been shown to be distributed uniformly throughout the lung unless there is localized abnormality of pulmonary blood flow.[24] In our group of patients biopsy tissue was taken from the lung of the systemic to pulmonary arterial shunt or from the lung periphery distal to large aortopulmonary collateral vessels. In one patient it was necessary to perform bilateral lung biopsies.

Morphometric assessment of the structure of the peripheral pulmonary arteries can be related to the degree of hemodynamic disturbance of the circulation. We now have a way to predict even minor degrees of elevation in pulmonary arterial pressure and resistance,[7] and this is particulary valuable if a patient is being considered for a Fontan-type surgical procedure.

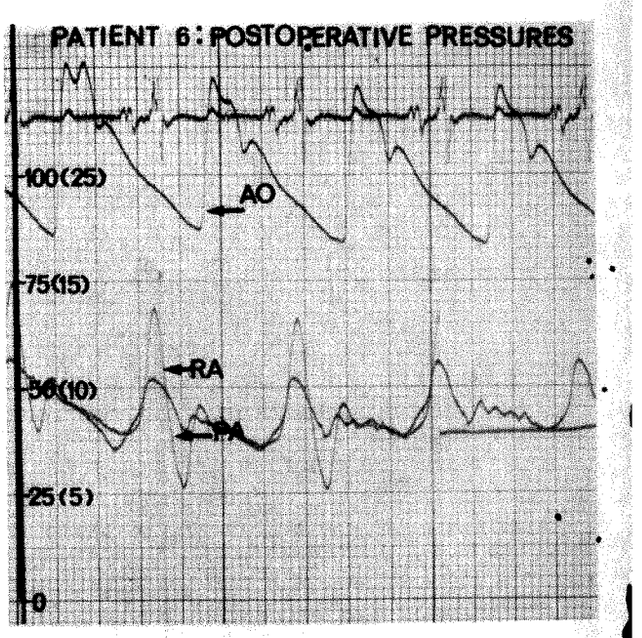

FIGURE 7. Patient 6. Postoperative pressure tracings. The electrocardiogram is at the **top.** The scale on the **left** shows calibrated values for aortic (AO) pressure, and in **parentheses** calibrated values for right atrial (RA) and pulmonary arterial (PA) pressure.

Acknowledgment

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Ventricular Septal Defect in Infancy: Detection With Two Dimensional Echocardiography

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To determine the sensitivity and specificity of two dimensional echocardiography in detecting ventricular septal defect two dimensional echocardiograms were performed on 53 infants under 1 year of age. The diagnosis of ventricular septal defect was confirmed by cardiac catheterization in 27 patients; an intact ventricular septum was confirmed by catheterization in 18 and clinically in 8. Using a 35° mechanical sector scanner with a 3.5 megahertz transducer, we imaged the ventricular septum in the long axis and in a four chamber view (apical or subcostal, or both). Images were recorded on videotape and reviewed independently by two observers unaware of the diagnosis. Interobserver agreement was 94 percent. Among the 27 patients with a ventricular septal defect, the lesion was correctly identified in 20 (74 percent) and was undetected in 7 (3 of whom had a defect less than 4 mm in diameter, as determined by angiography). No defect less than 4 mm in diameter was detected. Among the 26 patients with an intact septum, a defect was correctly excluded in 23 (88 percent); a false positive diagnosis was made in 3. The apical and subcostal views demonstrated the greatest number of defects (20 of 20), but also gave the highest number of false positive diagnoses (3 of 3). The long axis view was helpful when positive, but showed only 9 of 20 of the defects.

In this study, two dimensional echocardiography detected approximately three fourths of ventricular septal defects large enough to warrant cardiac catheterization in the 1st year of life. False positive diagnoses were related to dropout of echoes in the membranous septum when imaged in the four chamber views.

Ventricular septal defect is a common cause of congestive heart failure in the 1st year of life. Although M mode echocardiography demonstrates the general features of left ventricular volume overload—enlargement of the left atrium and left ventricle—it fails to provide reliable visualization of the defect itself. Several studies have suggested that two dimensional echocardiography is useful in the diagnosis of ventricular septal defect. King et al.[1] described visualization of ventricular septal defect with B scan ultrasonography. Seward et al.[2] utilized real time, wide angle sector echocardiography to demonstrate ventricular septal defect in 22 infants and children. These studies included relatively few infants under 1 year of age, and because a control group was not included, they did not address the question of specificity of echocardiography in the diagnosis of ventricular septal defect. More recently Bierman and Williams,[3] described visualization of ventricular septal defect using real time wide angle sector echocardiography in patients similar to those in our current study. They reported 89 percent accuracy in the detection of ventricular septal defect and 98 percent accuracy in the localization of the defect in infants under 1 year of age.

The present study was undertaken to determine the sensitivity and specificity of real time two dimensional echocardiography in the detection of ventricular septal defect. Because the majority of patients initially evaluated for ventricular septal defect are small infants, we confined the study to patients under 1 year of age.

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Methods

Study patients: Echocardiograms were obtained in 53 atients categorized into two groups on the basis of the presnce or absence of ventricular septal defect (Table I). Criteria or entry into the study were (1) a technically satisfactory two imensional echocardiogram with visualization of the venricular septum from at least two projections, and (2) confirmation of the presence of ventricular septal defect (by cardiac atheterization and angiography) or the absence of ventricular eptal defect (by either catheterization or clinical evaluaion).

The first group consisted of 27 infants with ventricular eptal defect, of whom 26 had a subcristal ventricular septal efect and 1 had a supracristal defect. Patients with an enocardial cushion defect and those with a muscular ventricular eptal defect were excluded from this study. The age of infants this group ranged from 1 day to 1 year (mean 4.7 months) nd their weight ranged from 2.7 to 10 kg (mean 4.7). Fifteen f these infants had only a ventricular septal defect; the reaining 12 had an associated defect: tetralogy of Fallot in 3; trial septal defect in 2, transposition of the great arteries in , double outlet right ventricle in 1 and valvular obstructive sions in 4.

The second group consisted of 26 infants with intact ventricular septum. This was confirmed by cardiac catheterizaon and angiography in 18 patients and clinically in 8. The ge of these patients ranged from 1 day to 1 year (mean 3.5 onths) and their weight ranged from 3.1 to 12.2 kg (mean .7). Of the 26 patients in this group, 14 had normal cardiac natomy; total anomalous pulmonary venous return, transosition of the great arteries and aortic stenosis were each resent in 3 patients, and coarctation of the aorta, atrial septal efect, and single atrium were each present in 1 patient. Of he six infants with normal cardiac anatomy undergoing cariac catheterization, five had cardiac arrhythmia and one had vascular ring.

Two dimensional echocardiography: Two dimensional hocardiograms were obtained using a model 513 Hoffrel 35° echanical sector scanner with a 3.5 megahertz transducer. he ventricular septum was imaged in a left parasternal long xis projection and in one or more four chamber views (apical r subcostal, or both). In the long axis view, the transducer was positioned at the third or fourth intercostal space, and the sector beam scanned the left ventricle from the apex to the aortic root (Fig. 1). The four chamber views were performed from the cardiac apex, the subxiphoid area and from points between these locations depending on where the optimal image of the ventricular septum could be obtained (Fig. 2 and 3). In this paper, we have used the term "subcostal" in referring to the projections obtained from beneath the ribs and xiphoid process in general, and the term "subxiphoid" when the image was obtained from the subxiphoid are in particular.

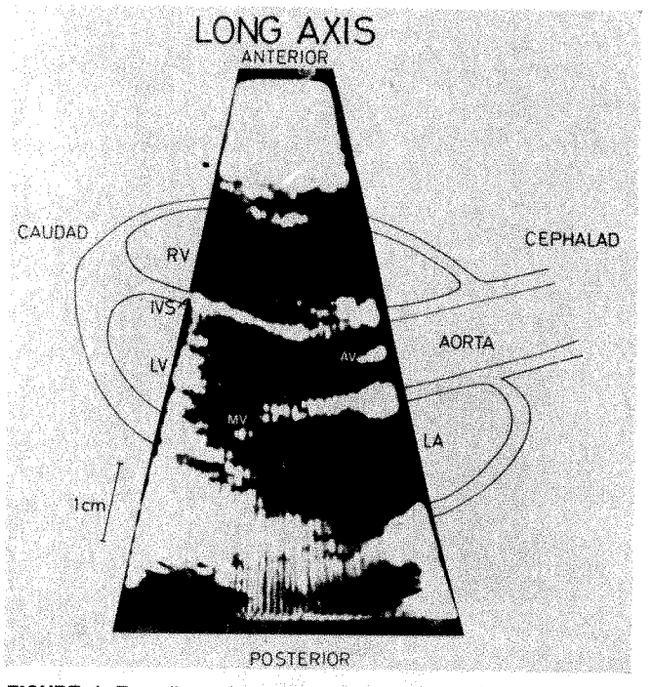


FIGURE 1. Two dimensional echocardiogram obtained using a left parasternal long axis projection in a normal infant. The figure is oriented with the subject's head to the observer's right and the feet to the left. The right (RV) and left ventricles (LV) are apparent, as well as the left atrium (LA), mitral valve (MV) and aortic valve (AV). The interventricular septum (IVS) is intact and continuous with the anterior aortic root.

The scans were permanently recorded on 0.5 inch (1.27 cm) videotape for future analysis. Subsequently, the videotapes were viewed and scored independently by two observers as to the presence or absence of ventricular septal defect. The tapes were viewed randomly without knowledge of the patient's identity or diagnosis. Interobserver agreement was 94 percent. In the case of disagreement, the decision of the more experienced observer was used in the final analysis of results.

ABLE I

o Dimensional Echocardiograms in Infants Less Than 1 ear of Age

Patients With Ventricular Septal Defect (n = 27)		Patients With Intact Ventricular Septum (n = 26)	
Subcristal	26	Catheterization	18
Supracristal	1	Clinically	8
ge 1 day–1 yr (mean 4.7 mo)		Age 1 day–1 yr (mean 3.5 mo)	
Veight 2.7–10 kg (mean 4.7)		Weight 3.1–12.2 kg (mean 4.7)	
lo associated defect	15	Normal cardiac anatomy	14
ssociated defect		Cardiac defect	
ToF	3	TAPVR	3
ASD	2	TGA	3
TGA	2	AS	3
DORV	1	Coarctation	1
Valve obst lesions	4	ASD	1
		Single atrium	1

AS = aortic stenosis; ASD = atrial septal defect; DORV = double itlet right ventricle; TAPVR = total anomalous pulmonary venous turn; TGA = transposition of great arteries; ToF = tetralogy of Fallot; alve obst lesions = valve obstructive lesions.

Results

Sensitivity of two dimensional echocardiography: Ventricular septal defect was correctly detected in 20 of the 27 patients with a proved defect. The diameter of the defect, as estimated from the angiograms, ranged from 4 to 12 mm (mean 7). In seven patients the defect was not visualized in the two dimensional echocardiogram. Thus, the sensitivity of echocardiography in the detection of ventricular septal defect in this group of patients was 74 percent. The defects undetected by echocardiography ranged from 3 to 10 mm in diameter, and three measured less than 4 mm in diameter. In the

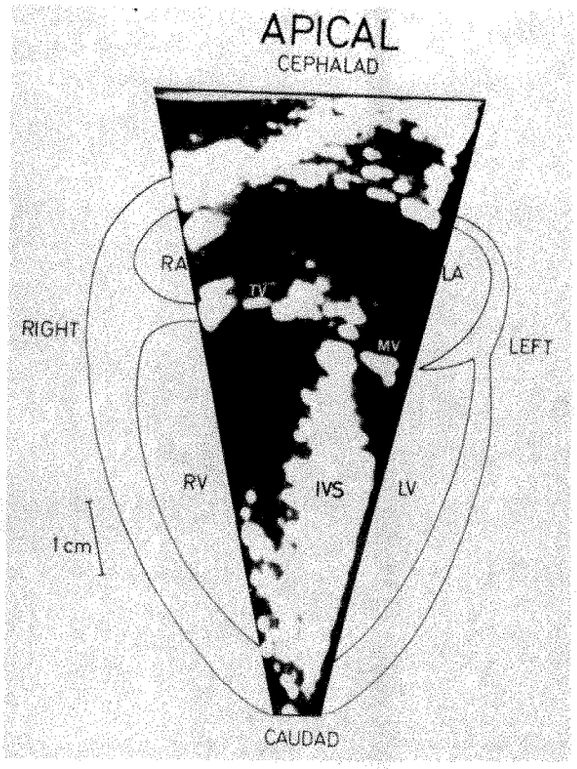


FIGURE 2. Two dimensional echocardiogram from the cardiac apex of a normal subject. The left-sided structures are to the observer's right, and the right-sided structures are to the left, similar to a four chamber angiographic projection. The right ventricle (RV), left ventricle (LV), right atrium (RA), left atrium (LA), tricuspid valve (TV) and mitral valve (MV) are visualized. The intact interventricular septum (IVS) is vertical in this projection, and runs parallel to the ultrasonic beam.

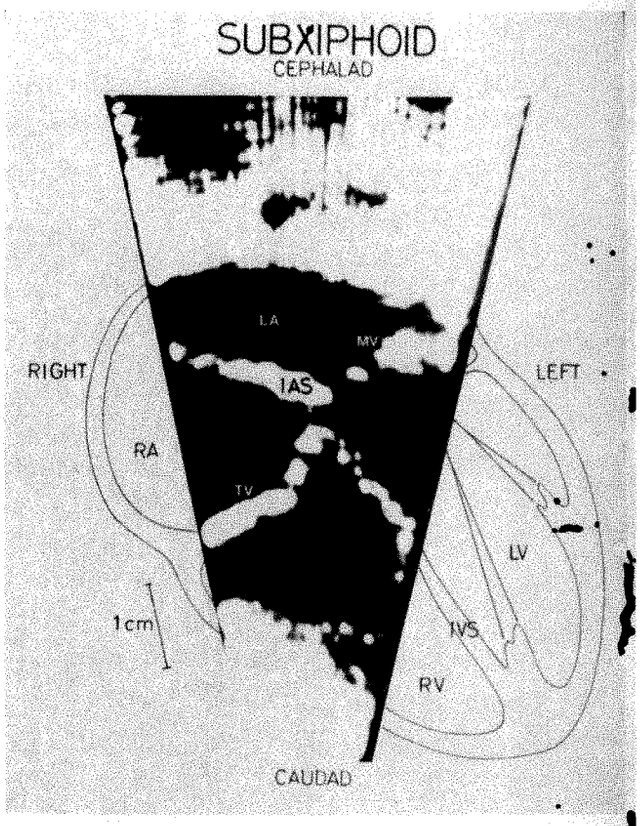


FIGURE 3. Normal two dimensional echocardiogram obtained from the subxiphoid area. The anatomy is similar to the apical projection and the structures are labeled accordingly. The intact interatrial septum (IAS) is imaged in this infant. The interventricular septum (IVS) is also intact and lies in a more transverse position than in the apical view. Abbreviations as in Figure 2.

subgroup of 15 patients with an isolated ventricular septal defect, the defect was correctly visualized in 11. The sensitivity within this subgroup was 73 percent. There was no significant difference in the sensitivity of detection of ventricular septal defect between patients with an isolated defect and those with an associated intracardiac defect.

Specificity of two dimensional echocardiography: Intact ventricular septum was correctly identified in 23 of the 26 infants with a proved intact septum. A false positive diagnosis of ventricular septal defect was made in three patients, two of whom had normal cardiac anatomy and one aortic stenosis. Thus, the specificity was 88 percent. In the 14 infants with normal cardiac anatomy, intact ventricular septum was correctly identified in 12 (specificity 86 percent). Thus, there was no significant difference in the specificity in visualization of intact ventricular septum between patients with various forms of congenital heart disease and those with normal intracardiac anatomy.

Long axis view: This projection demonstrated only 9 of the 20 defects that were detected with echocardiography in the 27 infants with ventricular septal defect (Fig. 4). Of the nine patients, eight had a subcristal ventricular septal defect, including the three patients with tetralogy of Fallot and the one infant with double

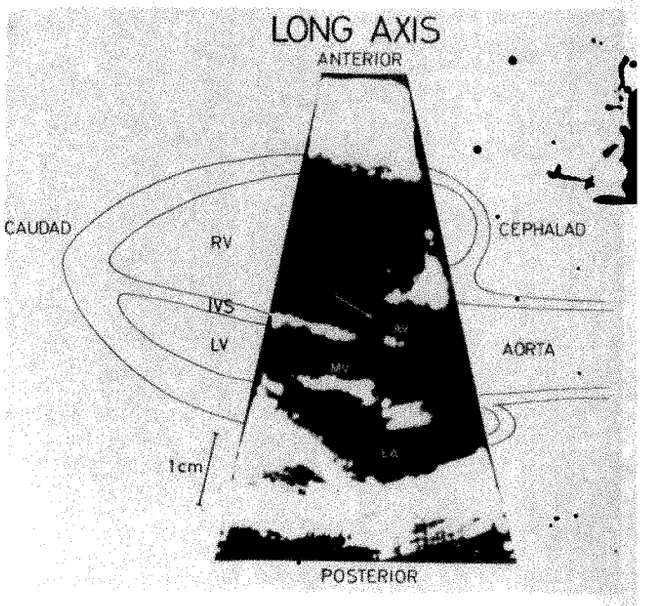
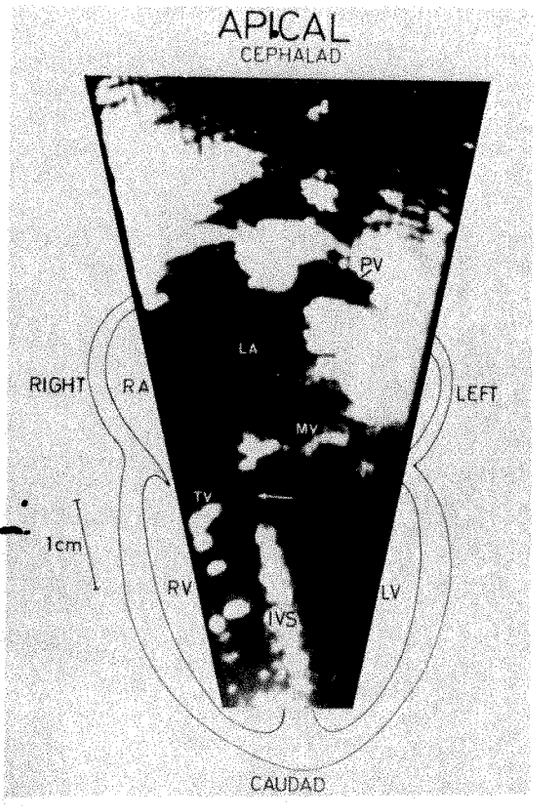
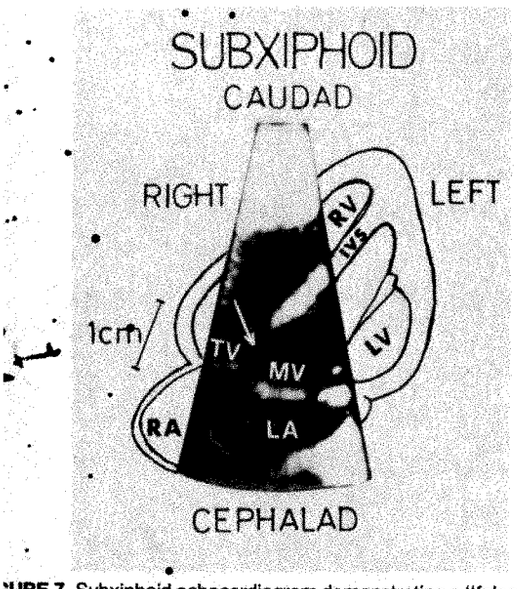


FIGURE 4. Two dimensional echocardiogram demonstrating the ventricular septal defect in a patient with tetralogy of Fallot (left parasternal long axis view). The defect (**arrow**) is seen immediately beneath the aortic root. Abbreviations as in Figure 1.



GURE 5. Apical four chamber view demonstrating the ventricular ptal defect (**arrow**) in an infant. A pulmonary vein (PV) is shown en- ing the left atrium (LA). Unidentified abbreviations as in Figure 2.



GURE 7. Subxiphoid echocardiogram demonstrating a "false positive" ıtricular septal defect. There appears to be a defect in the upper tion of the ventricular septum (**arrow**), immediately beneath the ınection of the mitral (MV) and tricuspid valve (TV) tissue. However, defect was identified at cardiac catheterization in this infant with ıgenital complete atrioventricular block. In this illustration, obtained fore modification of our ultrasonic equipment, the caudal and phalad orientation (but not the left-right relation) is reversed compared h that in the other illustrations. Thus, the apex is at the upper right ner of the figure. Unidentified abbreviations as in Figure 3.

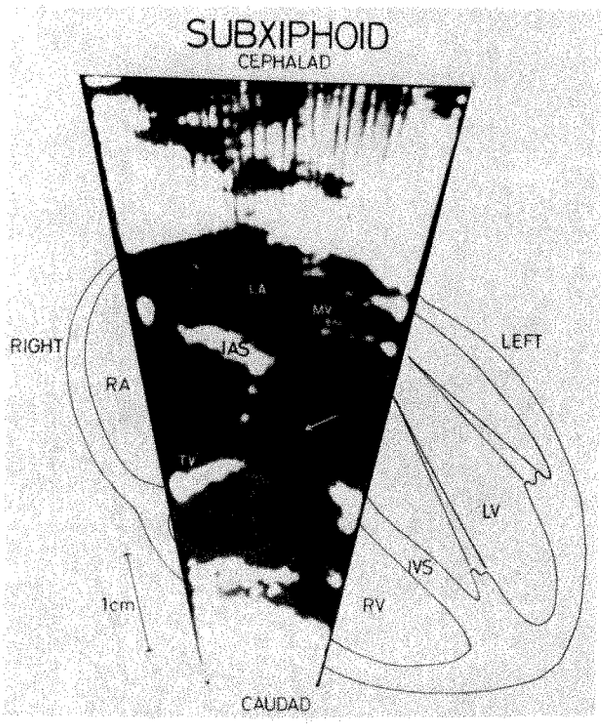


FIGURE 6. Subxiphoid view demonstrating a large ventricular septal defect (**arrow**) in a 3 month old infant. A secundum atrial septal defect was also demonstrated at cardiac catheterization and is seen here as a defect in the interatrial septum (IAS). Unidentified abbreviations as in Figure 3.

outlet right ventricle. The supracristal ventricular septal defect was also correctly diagnosed in this view. There was no false positive diagnosis using this projection.

Four chamber projections (apical and subcostal): These views demonstrated each of the 20 defects that were visualized in the 27 infants with ventricular septal defect (Fig. 5 and 6). However, these views also yielded the only three false positive diagnoses in the 26 patients with intact ventricular septum. In each of these infants, there appeared to be a defect in the upper portion of the ventricular septum, immediately below the connection of mitral and tricuspid valve tissue with the inferior portion of the atrial septum (Fig. 7).

Discussion

Factors affecting sensitivity of method: Two dimensional echocardiography appears to be useful in the diagnosis of ventricular septal defect in small infants. In the present study, we were able to demonstrate the defect in three fourths of the patients studied, with a false positive rate of 12 percent. It is apparent that several factors affect the sensitivity of two dimensional echocardiography in detection of ventricular septal defect:

1. *The resolution of the ultrasonic equipment.* In vitro studies in our laboratory[4] have indicated that a 3 mm diameter defect in a strip of canine myocardium is

the smallest size that can be consistently visualized with our ultrasound equipment. In the present study, the smallest defect correctly identified was 4 mm in diameter, and defects of 3.0, 3.0 and 3.5 mm were undetected. Improvements in resolution may be possible with transducers of higher frequency.

2. *The anatomic location of the defect.* A defect in the anterior portion of the septum, as in tetralogy of Fallot, is easily demonstrated in the long axis projection. In addition, a false positive diagnosis is uncommon in this view. The four chamber views (apical and subcostal) appear particularly helpful in the detection of subcristal ventricular septal defect without an overriding aorta. However, in these projections, the ultrasonic beam is in a parallel rather than in a perpendicular orientation with relation to the septum, and "dropout" of nonreflected echoes is more likely to occur. Thus, these projections were subject to false positive diagnoses of ventricular septal defect.

3. *The composition of the study group.* In a study group consisting of patients with tetralogy of Fallot or infants with a large ventricular septal defect, the sensitivity and specificity of two dimensional echocardiography may approach 100 percent. Conversely, among patients with a ventricular septal defect less than 3 mm in diameter, the sensitivity will no doubt be lower.

4. *Skill and bias of the ultrasonographer.* Unfortunately, interpretation of two dimensional echocardiograms is partially subjective. A ventricular septal defect may be undetected if appropriate areas of the septum are not imaged. Likewise, it is more likely to be diagnosed by a physician-ultrasonographer aware of clinical findings such as congestive heart failure or a holosystolic murmur. In the present study, we attempted to eliminate the latter source of bias by interpreting the videotapes without knowledge of the patient's identity or clinical status.

Enhancement of diagnostic accuracy: Although one view may appear more sensitive or specific than another, we recommend that all projections be utilized in evaluating the infant with suspected ventricular septal defect. In addition to the views used in this study, Bierman and Williams[3] recently utilized a subxiphoid sagittal projection with excellent results in the detection and localization of ventricular septal defect in infants. Muscular ventricular septal defects are difficult to detect with any of the customary projections.[2,3] Pulsed Doppler echocardiography may assist in the detection of defects in the muscular portion of the septum,[5] and may be particularly useful when combined with two dimensional echocardiography.

Clinical implications: Two dimensional echocardiography is a useful adjunct to the noninvasive evaluation of the child with possible ventricular septal defect. It appears most useful in cases in which a large defect may be masked by the presence of other cardiac anomalies (for example, transposition of the great arteries). However, the technique must be used in conjunction with other clinical studies and with the realization that false positive and false negative diagnoses occur. In particular, the technique has limited value in evaluation of the child whose ventricular septal defect is small and thus possibly below the limits of resolution of existing ultrasonic equipment.

Acknowledgment

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Postnatal Endocardial Fibroelastosis of the Valve of the Foramen Ovale

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The valve of the foramen ovale of the heart changes at birth from a prenatal shunting device for the transseptal flow of systemic venous return to a postnatal active barrier to backflow of left atrial blood at higher pressure. To investigate the morphologic response to this functional change in the valve of the foramen ovale, we examined 200 hearts from embryos, fetuses and autopsy patients spanning over a millionfold range of heart weights (0.001 to 1,230 g). The relation of valve thickness to log heart weight was studied by a stepwise linear regression procedure that fitted the data to two linear regressions, one including observations made before birth and the other including observations made after birth. Analysis of variance tables demonstrated that the data are significantly better explained ($p < 0.001$) by two linear regressions that abruptly separate from one another at the time of birth than by a single linear regression. Histologic study showed that the prenatal valve consists of a thin myocardial layer with delicate endocardium. The postnatal thickening of the valve tissue occurs mainly by fibroelastotic thickening of the endocardium. The endocardial fibroelastosis of the valve develops after it closes and becomes a component of the left atrial wall. The observations support the concept that fibroelastosis is a nonspecific response of the lining of the cardiovascular system to increased mural tension.

The pathogenesis of endocardial fibroelastosis has been controversial. Its occurrence had been variously considered a reaction to inflammation, a congenital defect, the result of lymphatic obstruction, a response to hypoxia or the consequence of a metabolic defect, but most of these notions have been discredited.[1] Alternatively, the variety and nature of the settings in which fibroelastosis is observed have led to the concept that it may be a nonspecific stereotyped response of the cardiovascular lining layers to states of increased mural tension.[2–4]

Normal atrial endocardium has a histologic structure that is identical to the fibroelastosis found in pathologic states. In this study we examined the endocardial changes that occur on that component of the septum primum that forms the valve of the foramen ovale. The orifice of the foramen ovale of the heart is surrounded by the tissues of the atrial septum secundum. In the normal developing heart before birth, this orifice is guarded on its left side by a portion of the atrial septum primum, the valve of the foramen ovale. After birth there is functional closure of the valve as the pressure in the left atrium increases relative to that in the right. In changing from a passive structure in the transseptal bloodstream into a barrier of the orifice of the foramen ovale, the valve becomes subject to the tension that acts on the atrial wall. The principal determinants of mural tension at any point are intracavitary pressure and the wall curvature.[5]

To evaluate the nature of the postnatal thickening of the valve of the foramen ovale, human hearts spanning over a millionfold range of heart weights were examined. The relations between age, heart weight, foramen patency, thickness of the valve and histologic structure were studied.

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Methods

Preparation of hearts: To provide a wide range of material, human hearts from several sources were examined. Seventeen normal human embryos and fetuses ranging from stage 14 to 45 mm crown-rump length had been prepared by serial histologic sections. Details of the preparation, staining and staging of the embryos and three fetuses have previously been given.[6] Heart weights for these specimens were estimated from the size of the heart as seen on sections, and ranged from 0.001 to 0.08 g.[7] For these specimens, the thickness of the valve of the foramen ovale was measured from the histologic sections using a calibrated micrometer in the microscope ocular. Eleven fetuses of gestational ages 21 to 39 weeks were dissected, and heart weight was determined directly. The thickness of the valve of the foramen ovale was determined as before on histologic sections of the heart. The gestational age of the fetuses was estimated from the body size.[8]

The hearts of 26 stillborns and newborns up to 30 days of age, 18 infants up to 1 year of age and 28 children 1 to 15 years of age examined at autopsy at The Johns Hopkins Hospital were studied. The thickness of the valve of the foramen ovale was determined by direct measurement on the specimen using a micrometer calibrated to 0.01 millimeter. The diameter of the patent orifice, if present, was measured with an aluminum cone calibrated for millimeters of diameter. Blocks were taken from the interatrial septum of each specimen and processed routinely, sectioned at 5 μ, and examined after hematoxylin-eosin and Verhoeff-van Gieson elastic staining.

The hearts of 100 adults that had been examined after postmortem coronary arteriography and fixation in a distended state[9] were also studied as described. Among the 100 patients; 50 had no clinical or pathologic evidence of cardiac disease; the remaining 50 had cardiac enlargement secondary to a variety of disorders.

The patency of the foramen ovale was determined in all cases. When possible the diameter of its orifice was measured.

Data analysis: The valve thickness measurements were summarized both by ordinary descriptive statistics (mean ± standard error) and by a stepwise linear regression technique designed to highlight abrupt changes in the pattern of valve growth that might take place at birth. The valve thickness data were fitted initially to a simple linear regression with log age as the independent variable. The data were then partitioned into two subsets: one containing observations up to and including birth, and the other containing observations taken after birth. Two pairs of least squares linear regressions were fitted to these partitioned data. The first pair of regressions was constrained to have the same slope but arbitrary intercepts. The second pair was not constrained: Both slopes and intercepts were arbitrary. An analysis of variance (ANOVA) table was prepared in the usual manner.[10] The presence of a significant F value for the constrained regression pair would suggest that two parallel linear regressions better describe the data than does a single regression. A significant F value for the unconstrained regression pair would suggest that two arbitrary linear regressions better describe the data than do two parallel regressions.

Results

Histology: The principal findings in the various groups of hearts are given in Table I. Histologically (Fig. 1 and 2) the valve of the foramen ovale in the embryo and fetus is composed of a few cardiac muscle cells and two thin layers of endocardial tissue. At birth the muscle content of the valve has increased and is responsible for almost the entire thickness of the valve. The endocardial tissue at this time is a delicate layer. After birth, there is a dramatic increase in the thickness of the endocardium, which produces the majority of the increased thickness of the valve. This endocardial proliferation occurs on both sides of the valve and is characterized by formation of fibroelastotic laminae. There is also an increase in the myocardial component of the valve as the result of enlargement of cardiac muscle cells.

TABLE I
Heart Weight, Valve Thickness and Foramen Ovale Patency by Age Groups

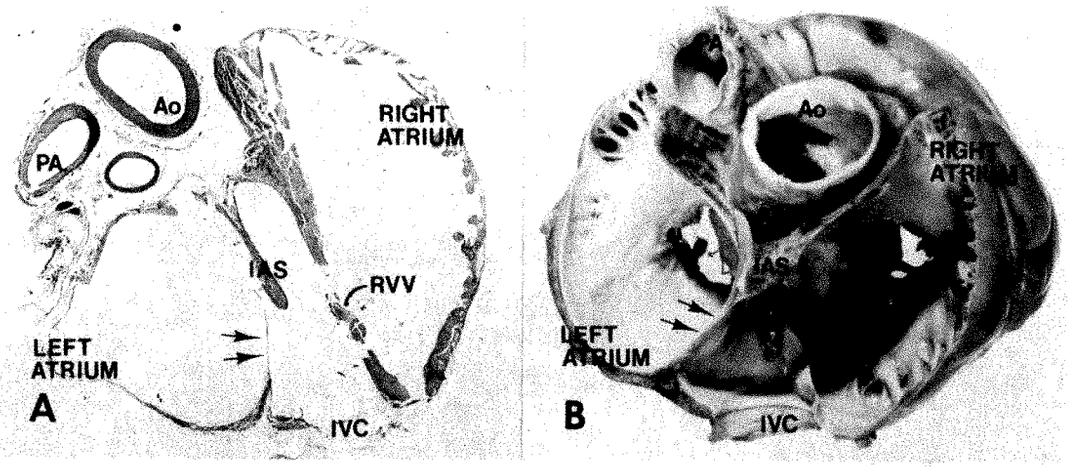
	n	Heart Weight* (g)	Thickness* of Valve of Foramen Ovale (mm)	Patent Foramen Ovale n	Patent Foramen Ovale (%)
Embryos and fetuses (8 to 20 weeks)	17	0.8 ± 0.2	0.02 ± 0.002	17	(100)
Late fetuses (21 to 39 weeks)	11	8.3 ± 2.2	0.21 ± 0.04	11	(100)
Newborns (birth to 1 month)	26	13 ± 1.2	0.33 ± 0.03	13	(100)
Infants (1 month to 1 year)	18	40 ± 4.8	1.33 ± 0.09	10	(56)
Children (1 to 15 years)	28	131 ± 18	1.10 ± 0.06	4	(14)
Adults, normal hearts (over 15 years)	50	292 ± 8.1	1.18 ± 0.05	11	(22)
Adults, hypertrophy (over 15 years)	50	694 ± 35	1.15 ± 0.06	5	(10)
Total	200	250 ± 21	0.91 ± 0.04	84	(42)

* Values expressed as mean ± standard error of the mean.

Relation of thickness of valve of foramen ovale to heart weight (Fig. 3): During intrauterine life, which corresponds to a heart weight of less than 15 g, there is a slight and progressive increase in valve thickness, which corresponds to the increasing heart weight of fetal growth. During the increase in heart weight from 15 to 40 g, there is a dramatic increase in valve thickness. The range of heart weights between 15 and 40 g corresponds to the 1st months of life and the rapid increase in valve thickness in this weight distribution corresponds to the increase observed in postnatal life.

Relation between thickness of valve of foramen ovale and age (Fig. 4): There is a slight and gradual increase in thickness during the last 5 months of gestation. The average thickness of the valve at birth is 0.33 mm. Beginning immediately with birth and continuing until 6 months of age, there is a very rapid increase in the amount of valve tissue. After 6 months of age there is some variability in valve thickness, but there is no apparent increase in valve tissue after the initial rapid increase, and the thickness of the valve increases only slightly throughout life.

Valve thickness as a function of heart weight and age: Table II shows the analysis of variance table for the



IGURE 1. **A**, histologic section through the atria of the heart of a fetus. The valve (**arrows**) allows blood to pass through the patent foramen ovale the interatrial septum (IAS) from the right to the left atrium. The right venous valve (RVV) or the valve of the inferior vena cava (IVC) tends to rect venous return toward the septum (Verhoeff-van Gieson elastic stain X9, reduced by 33 percent). **B**, adult heart, sectioned as in **A**, and viewed om the atrial aspect. The valve of the foramen ovale (**arrows**) is an integral structural component of the interatrial septum. Ao = aorta; PA = pulmonary tery.

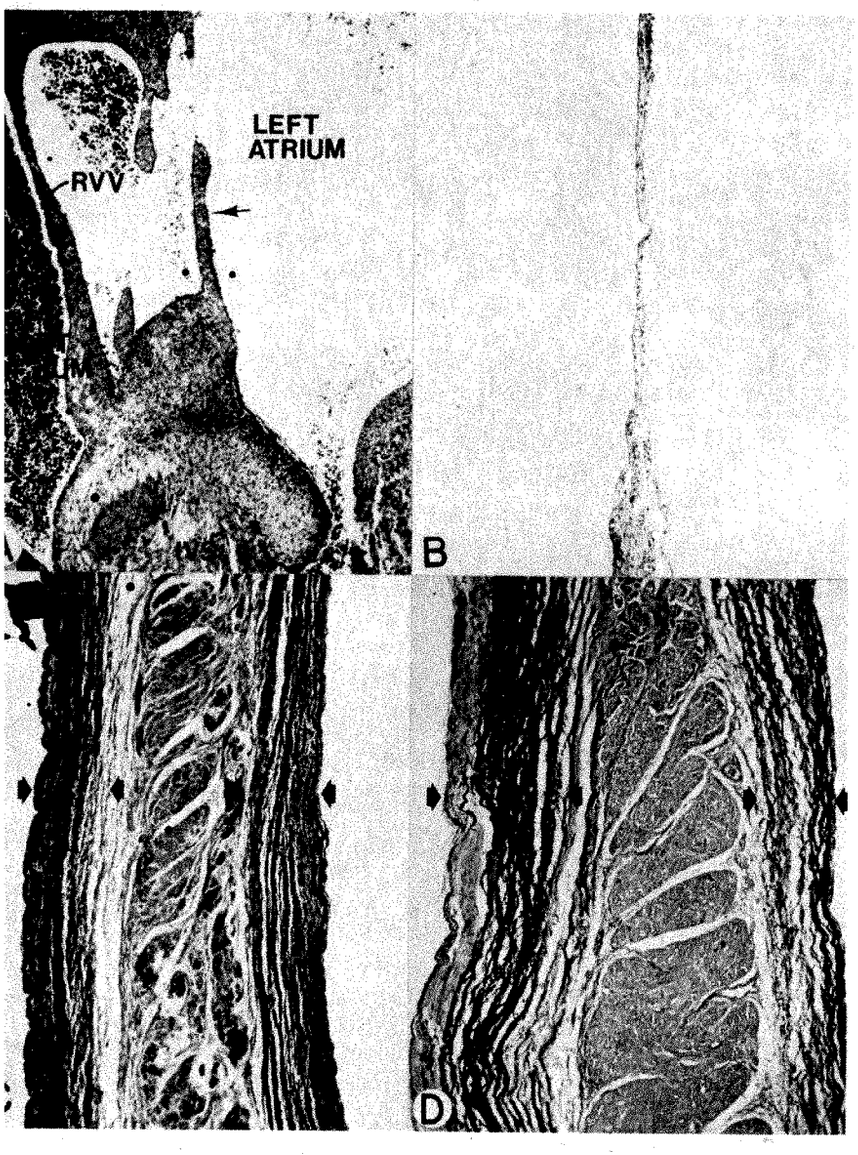


FIGURE 2. Valve of the foramen ovale at different stages of development. In the embryo (**A**) and fetus (**B**) the valve (**arrow**) is delicate with a thin endocardial layer and a few myocytes. In a child (**C**) and adult (**D**) the valve has become a component of the atrial wall and has endocardial fibroelastosis (**between arrows**) on both sides as well as a thicker myocardial layer. IVS = interventricular septum. (All Verhoeff-van Gieson elastic stain X90, reduced by 33 percent.)

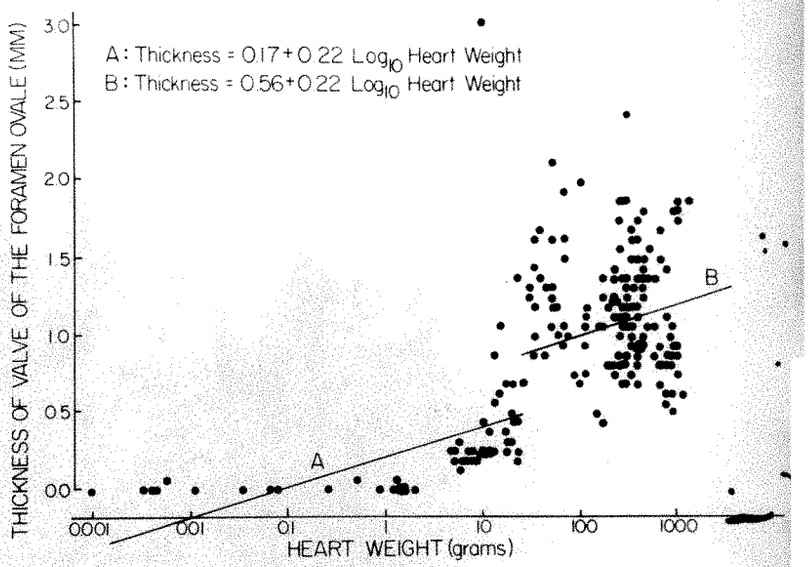


FIGURE 3. Thickness of the valve of the foramen ovale as a function of log heart weight. Slope of the double linear regression equation, identical for the prenatal subset (**A**) and the postnatal subset (**B**), is significant ($p < 0.001$). The intercept difference for prenatal and postnatal subsets is significant ($p < 0.005$).

regression of valve thickness as a function of log age, partitioned into prenatal and postnatal subsets. The regression consisting of a separate linear regression for each subset, constrained to the same slope, fitted significantly better ($p < 0.001$) than either a single linear regression (no partitioning) or no regression (that is, zero slope). However, when the separate linear regressions were allowed to have distinct slopes, no significant additional variance was explained. The common slope of this least squares fit was 0.22, with an intercept of −0.18 for the prenatal subset and 0.43 (= −0.18 + 0.61) for the postnatal subset (Fig. 4). Both regression coefficients (slope coefficient with respect to age and subset coefficient) were highly significant ($p < 0.001$), and the standard errors were small with respect to their corresponding coefficients. Similar results were obtained with log heart weight as the independent variable. These

TABLE II
Analysis of Variance for Regression of Valve Thickness as a Function of Log Age, Partitioned Into Prenatal and Postnatal Subsets

Source	DF	Sum of Squares	F	p
Total	199	59.17		
Regression	2	26.74	81.23	<0.001
Error	197	32.43		

Independent Variable	Coefficient	Standard Error	F*	p
Intercept	−0.18			
Log_{10} age	0.22	0.04	30.61	<0.001
Subset (prenatal = 0, postnatal = 1)	0.61	0.10	34.81	<0.001

* Arbitrary intercepts and identical slopes for prenatal and postnatal subsets. Arbitrary slopes did not explain significant additional variance.

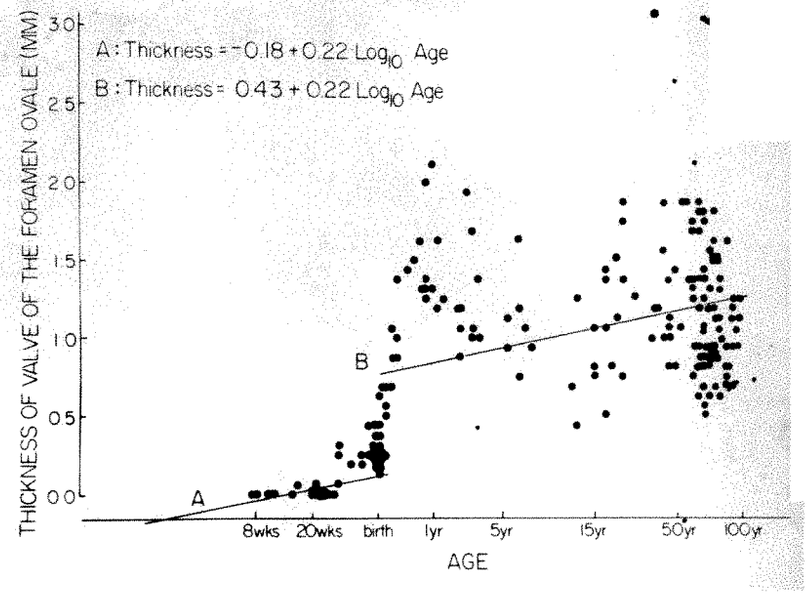


FIGURE 4. Thickness of the valve of the foramen ovale as a function of log age in weeks post-conception. The slope of the double linear regression equations, identical for the prenatal subset (**A**) and the postnatal subset (**B**), is significant ($p < 0.001$). The intercept difference for the prenatal and postnatal subsets is significant ($p < 0.001$).

findings demonstrate that the thickness of the valve of the foramen ovale increases slowly until birth, abruptly thickens in the newborn period, and then returns to a pattern of slow, steady increase.

Diameter and patency of foramen ovale: From 1 to 15 g of heart weight the diameter of the foramen ovale increases steadily from 1 to about 4 mm in diameter. For heart weights of 15 to 20 g, which correspond to heart weights at birth after 9 months' gestation, the mean diameter of the foramen ovale is 4.3 mm (range 3 to 6 mm). The earliest instance of complete anatomic closure occurred in a heart weighing 28 g from a 7 month old infant. The majority of the foramens were obliterated after 40 g of heart weight. In those specimens in which age was greater than 15 years, probe-patency of the foramen was demonstrated in 16 percent. There was no apparent association with age or heart weight. All specimens demonstrated sufficient valve tissue to prevent left to right intraatrial shunting of blood.

Discussion

Histology: The valve of the foramen ovale before birth is composed of a sheet of cardiac muscle cells and thin layers of endocardial tissue. At birth the muscle content has increased and accounts for most of the thickness of the valve, but the endocardial tissue remains as two thin layers. A few elastic fibers have appeared between the endothelial and collagen layers of the endocardium. Soon after birth the valve increases abruptly in thickness ($p < 0.001$). A prominent endocardial elastic layer develops, with an inner part composed of this network of fine elastic fibers and an outer part composed of thicker elastic fibers and fine collagen fibers. This dramatic growth of fibroelastic tissue results in a thick endocardium by the end of the 1st year. In the adult heart, subsequent changes in endocardial structure are minor and appear to be uninfluenced by cardiac hypertrophy or patency of the foramen ovale. Thus, the valve of the foramen ovale in the adult heart is formed by central muscle bundles and two thick endocardial surfaces. The thick endocardium is morphologically identical to the fibroelastosis found in the cardiovascular system in various disease states.

Endocardial fibroelastosis as a response to mural tension: Endocardial fibroelastosis has been associated with such diverse conditions as hypoplastic left heart syndrome, anomalous origin of the left coronary artery from the pulmonary trunk, idiopathic endocardial fibroelastosis, glycogen storage disease, coarctation of the aorta and myocardial infarction. Hypotheses on the origin of endocardial fibroelastosis have included hypoxia, lymphatic obstruction, increased cavity pressure, fibrin deposition or combinations of these factors.[1] Black-Schaffer[2] first suggested that idiopathic endocardial fibroelastosis is a response to the dilatation of the left ventricular chamber. Other morphologic evidence supports this concept that endocardial fibroelastosis is a nonspecific response to increased mural tension,[3,4] and intimal fibroelastosis in blood vessels has been similarly interpreted.[11] The magnitude of this mural tension, and the amount of fibroelastic connective tissue formed, appears to correlate with decreased curvature of the cavity and increased intracavitary pressure, consistent with the Laplace relation.[5] With postnatal closure of the foramen ovale on establishment of an increased pulmonary circulation, the valve becomes a component of the atrial wall and becomes subject to the same mural tension existing in other portions of the atrium. The valve usually becomes curved concave to the left atrium (Fig. 1B), probably because of the relatively higher pressure normally found on the left side of the heart. Presumably tension would be applied to the full thickness of the valve. No relation was discovered between patency of the foramen ovale and thickness or any histologic feature of the valve. The incidence of patency of the foramen ovale found in this group of hearts was somewhat less than that reported by others in the adult heart.[12–14]

In conclusion, examination of the valve of the foramen ovale in 200 hearts over a wide range of age and heart size showed a highly significant increase in valve thickness in the postnatal period ($p < 0.001$) caused by the development of endocardial fibroelastosis and an increase in myocardium in the valve. The increase in thickness occurs after the postnatal conversion of the valve from a free structure in the bloodstream to a tension-sustaining component of the atrial wall. The observations support the concept that fibroelastosis is a nonspecific response of the cardiovascular lining layers to increased mural tension.

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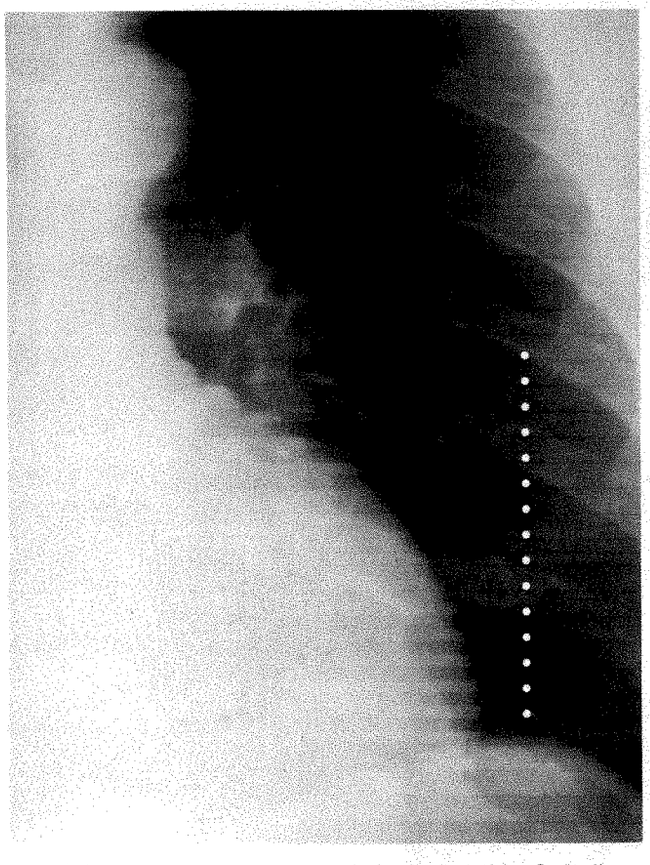

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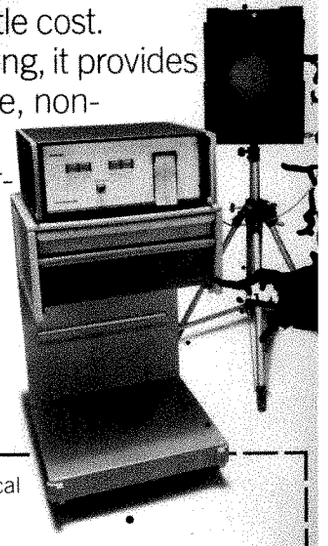

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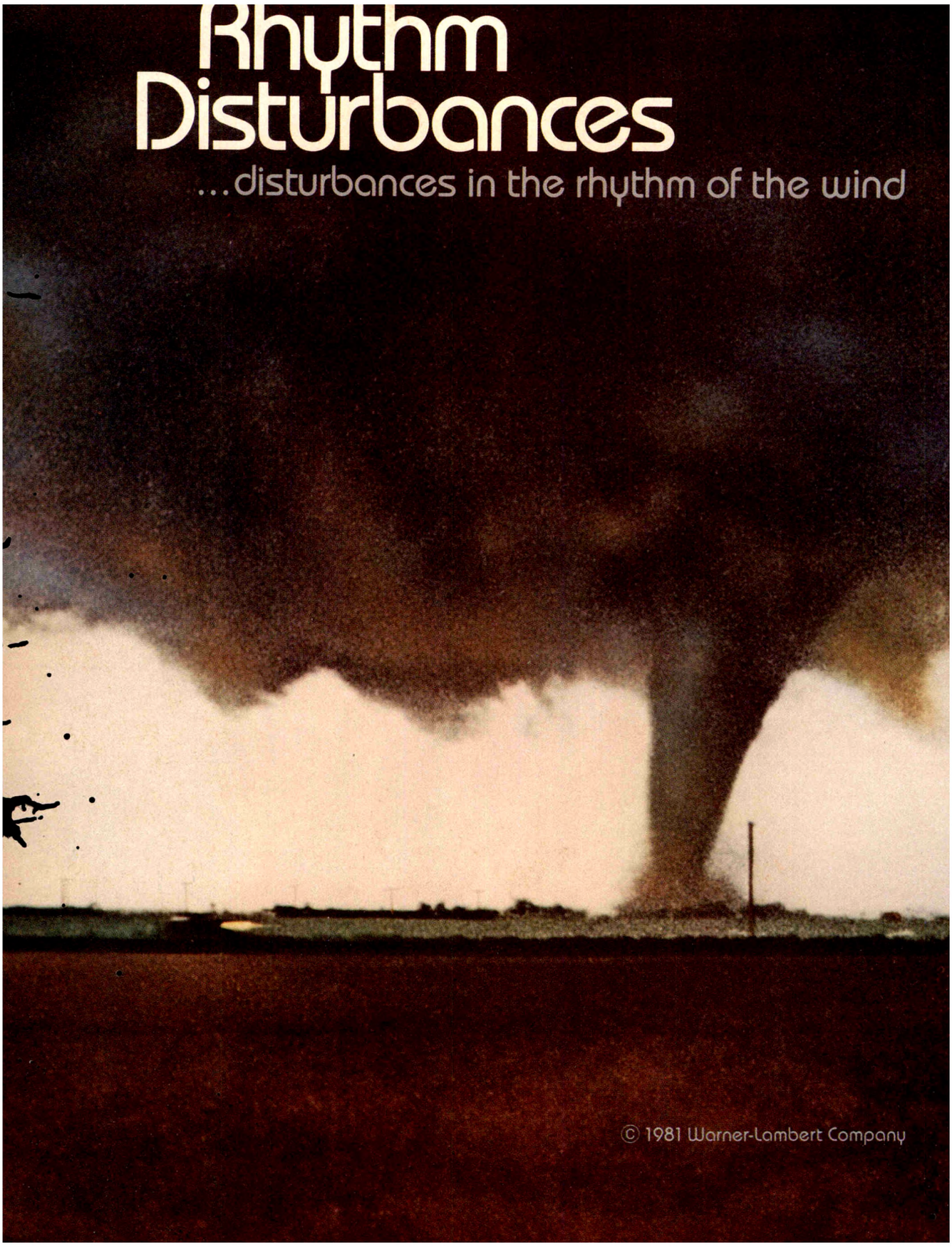
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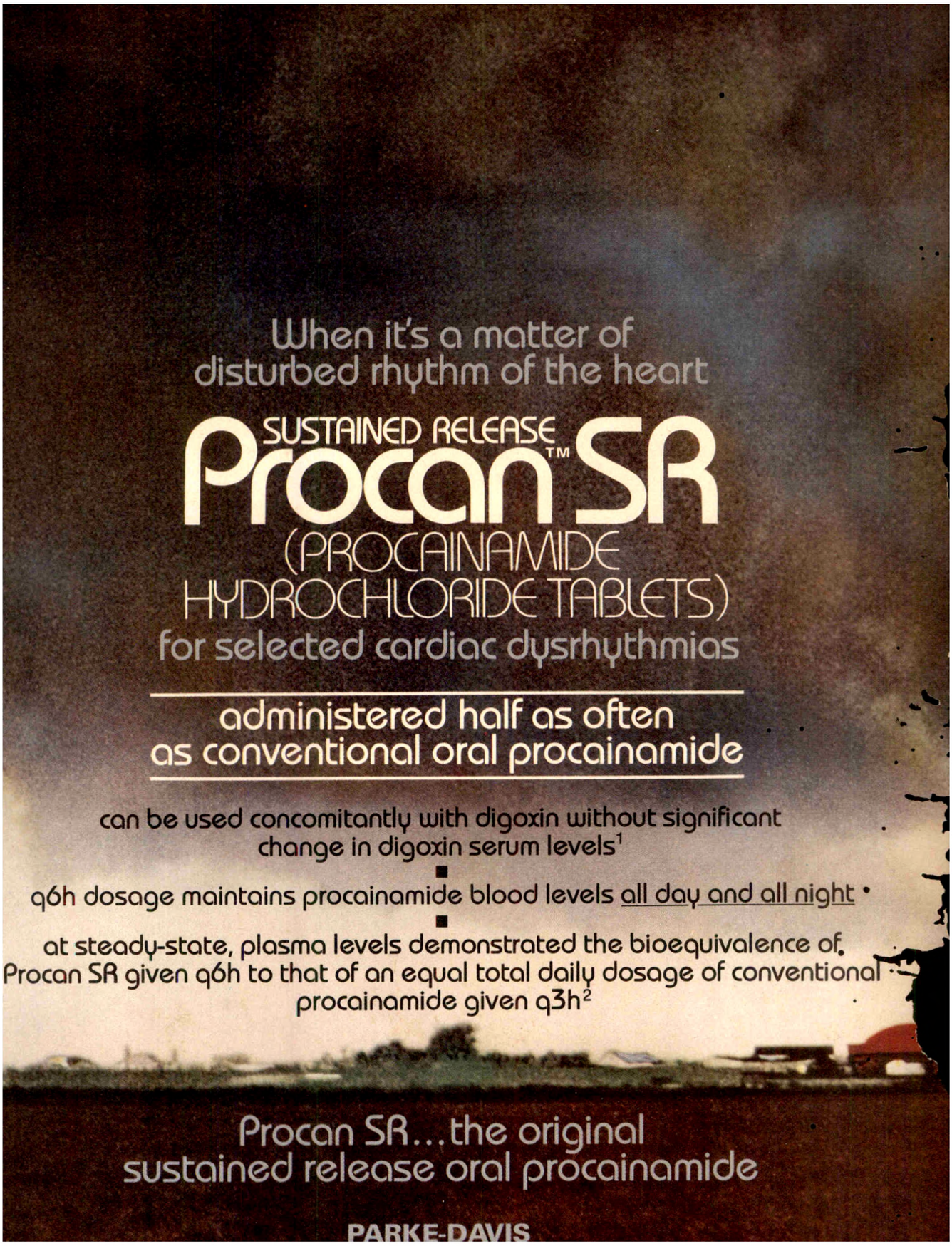
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The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient re-evaluated because asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney diseases, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome. Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patie receiving maintenance procainamide therapy.

ADVERSE REACTIONS: Hypotension following oral administrati is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reporte (see PRECAUTIONS). Reactions consisting of fever and chills hav also been reported, including a case with fever and chills plus nau sea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses c the drug. Bitter taste, diarrhea, weakness, mental depression, gidd ness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

Agranulocytosis has occasionally followed the repeated use of t drug, and deaths have occurred. Therefore, routine blood counts a advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tra infection. If any of these should occur, and leukocyte counts indica cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride tablets) are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every hours instead of the more frequent every-three-hour dosing interva required for standard preparations of oral procainamide hydrochlo ride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamic hydrochloride is recommended until the tachycardia is interrupted the limit of tolerance is reached. Maintenance may then be continu with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of stan dard procainamide hydrochloride followed thereafter by a total dai dosage of 50 mg/kg of body weight given at three-hour intervals. The suggested oral dosage for premature ventricular contractions 50 mg/kg of body weight daily given in divided doses at three-hou intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg c body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0. g every six hours; patients weighing between 55 and 91 kg (120 an 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (2 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia—Treatme with standard procainamide hydrochloride is recommended until th arrhythmia is interrupted or the limit of tolerance is reached. Mainte nance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Star dard procainamide hydrochloride may then be given at a dosage o 0.5 g to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every s hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

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References: 1. Leahey EB Jr, Reiffel JA, Giardina E-GV, et al: The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. *Ann Intern Med* 92:605-608, May 1980.
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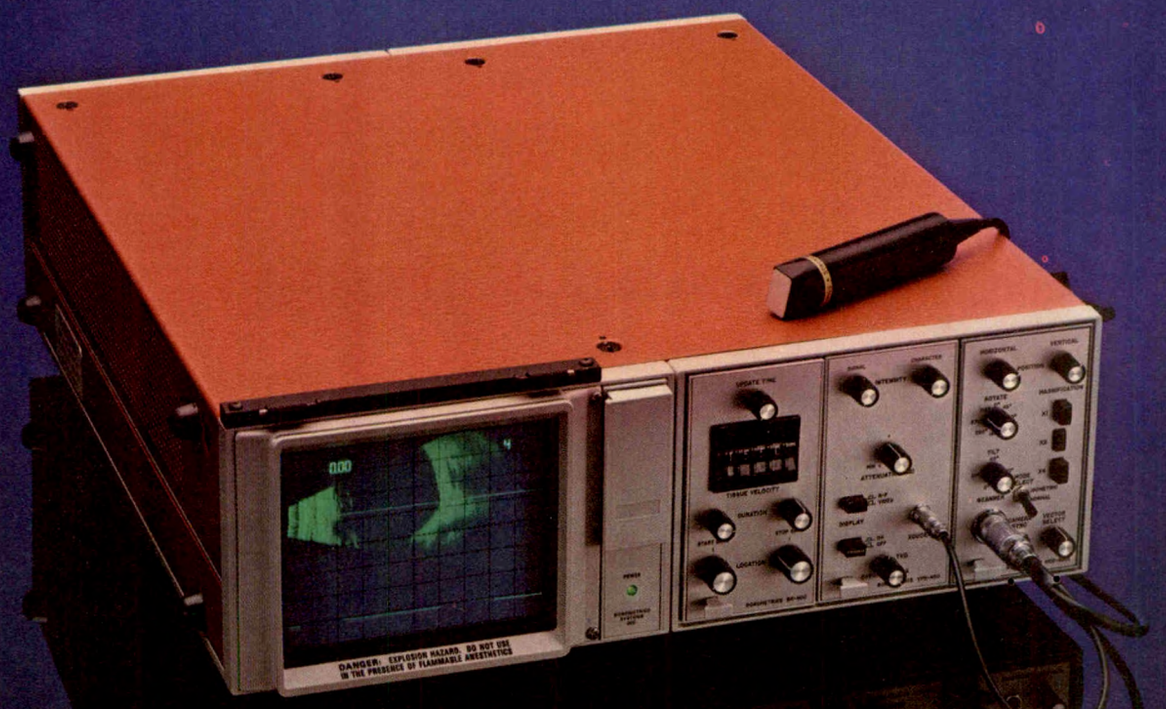

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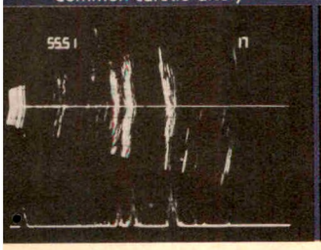

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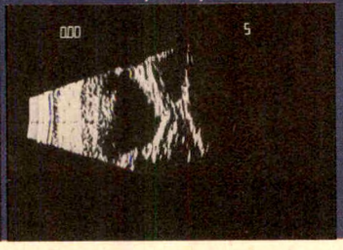

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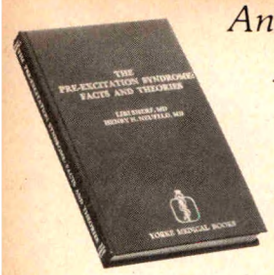

Announcing the comprehensive study of...the most fascinating syndrome in Cardiology...

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

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Henry N. Neufeld, M.D., FACC, Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

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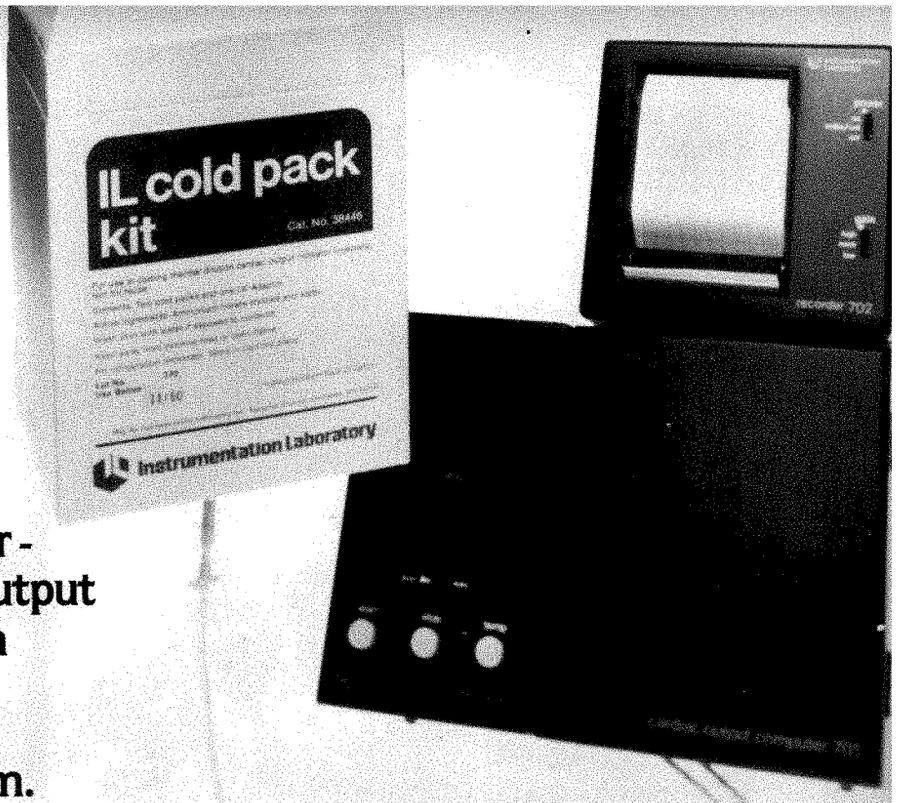

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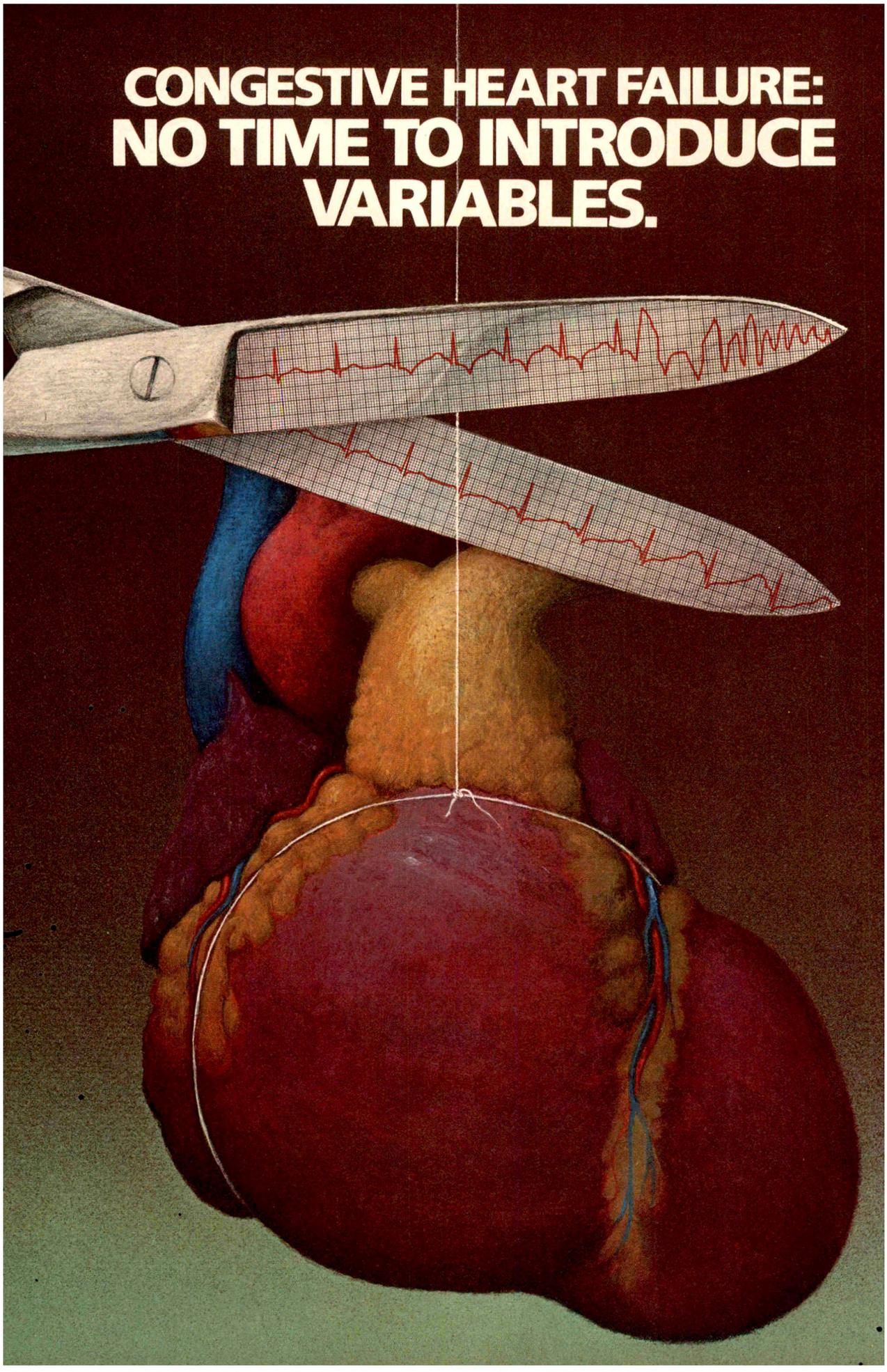

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Both digitalis and diuretics are almost always used in congestive heart failure. But both can cause serious cardiac arrhythmias.[1] Digitalis, because digitalization is one of the most precarious titrations in all of medicine. And diuretics, because diuretic-induced hypokalemia increases the vulnerability to digitalis toxicity.[2] See warnings and precautions in the brief summary of product information on the next page.

In serious congestive heart failure, the diuretic most frequently administered with digitalis is LASIX® brand of furosemide. However, the bioavailability of furosemide may be significantly altered by a change in tablet disintegrants and/or excipients.[3,4,5] And variations in the bioavailability of unlawfully-marketed furosemide tablets have produced unpredictable and serious clinical effects.[6]

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LASIX® is the original brand of furosemide. It is LASIX® that established the standard for furosemide performance. It is LASIX® that is the subject of almost 6,000 published papers. It is LASIX® that has been used successfully in millions of digitalized patients over the past 14 years. And it is LASIX® that has a remarkable quality-control record—almost 8 billion tablets manufactured without a single product recall.

LASIX® tablets are available in a dosage strength to meet almost every patient need—20, 40 and 80 mg.

Before prescribing, please consult complete product information, a summary of which appears on the following page.

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References: 1. Moe GK, Farah AE: Digitalis and allied cardiac glycosides, in Goodman LS and Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co, 1970, pp 653-682. 2. Smith TW: Digitalis: Ions, inotropy and toxicity, editorial. *N. Engl. J. Med. 299*:545, 1978. 3. Rubinstein MH, Eastwood BA, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: The effect of lubricant type and concentration on the bioavailability of furosemide from 80 mg tablets: *J. Pharm. Pharmacol. 30* (suppl.):12P, Dec. 1978. 4. Rubinstein MH, Price EF, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: In vivo evaluation of the effect of five disintegrants on the bioavailability of furosemide from 40 mg tablets: *J. Pharm. Pharmacol. 29* (Suppl.):5P, Dec. 1977. 5. Rubinstein MH, Rughani JM, School of Pharmacy, Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF, U.K.: The effect of four tablet binders on the bioavailability of furosemide from 40 mg tablets: *Drug Development and Industrial Pharmacy* 4(6): 541-553 (1978). 6. HEW News, publication 79-6, U.S. Department of Health, Education and Welfare (Food and Drug Administration), March 30, 1979, pp 2-3.

Rx Specify LASIX® brand of furosemide. To be sure the patient receives only LASIX®, take the steps necessary on your prescription to prevent substitution, in accordance with the regulations of your state.

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ONE LESS VARIABLE IN THE DIGITALIZED PATIENT

Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide). Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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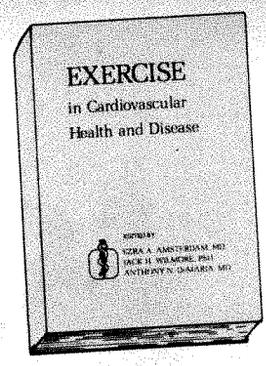

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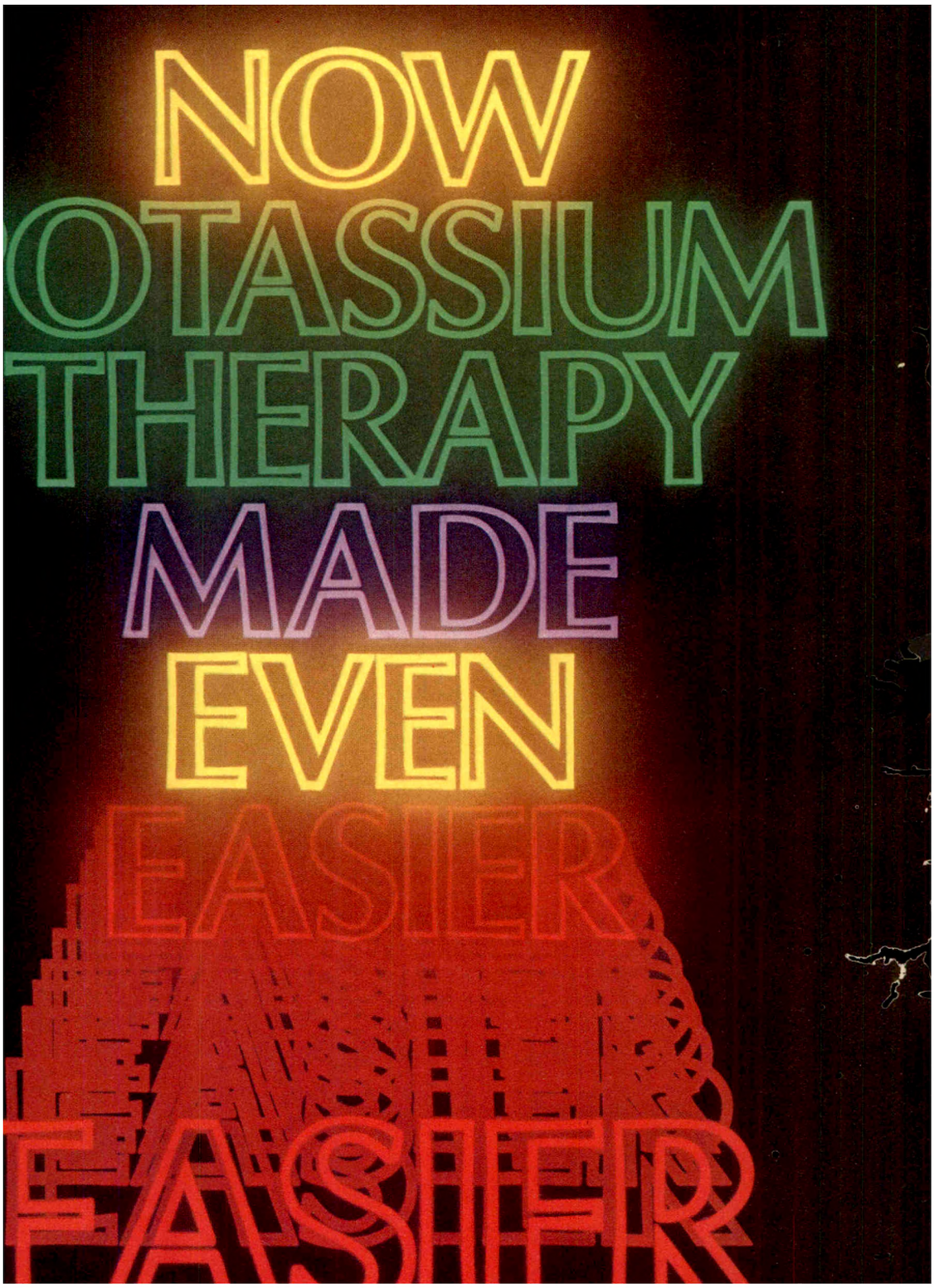
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Special wax-matrix delivery system permits gradual release of KCl over several hours to minimize high localized concentrations in the GI tract, thus minimizing the chance of GI irritation. The frequency of small bowel lesions with wax-matrix tablets is less than one per 100,000 patient years.

for patients who can't or won't take liquid supplements

Brief Summary

Description: Kaon Cl™-10 mEq is a sugar coated (not enteric-coated) tablet containing 1,750 mg potassium chloride (equivalent to 10 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control mild cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon Cl™-10 mEq (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) tha with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) case associated with wax-matrix tablets have been reported both in foreign countries and in th United States. In addition, perhaps because the wax-matrix preparations are not enteric coated and release potassium in the stomach, there have been reports of upper gastroir testinal bleeding associated with these products. The total number of gastrointestina lesions remains less than one per 100,000 patient years. Kaon Cl-10 mEq should be dis continued immediately and the possibility of bowel obstruction or perforation considered severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated wit an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassiur acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstratin hypokalemia in a patient with a clinical history suggesting some cause for potassium deple tion. In interpreting the serum potassium level, the physician should bear in mind that acut alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassiur while acute acidosis per se can increase the serum potassium concentration into the norma range even in the presence of a reduced total body potassium. The treatment of potassiur depletion, particularly in the presence of cardiac disease, renal disease, or acidosis require careful attention to acid-base balance and appropriate monitoring of serum electrolytes, th electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nau sea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation c the gastrointestinal tract and are best managed by diluting the preparation further, taking th dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings an Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretor mechanisms for potassium rarely causes serious hyperkalemia. However, if excretor mechanisms are impaired or if potassium is administered too rapidly intravenously, poten tially fatal hyperkalemia can result (see Contraindications and Warnings). It is important t recognize that hyperkalemia is usually asymptomatic and may be manifested only by a increased serum potassium concentration and characteristic electrocardiographic change (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the Q interval). Late manifestations include muscle-paralysis and cardiovascular collapse fron cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-2 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized o digitalis, too rapid a lowering of the serum potassium concentration can produce digitali toxicity.

Caution: Federal law prohibits dispensing without prescription.

How Supplied: Bottles of 100 and 500; Stat-Pak® (Unit-Dose) box of 100.

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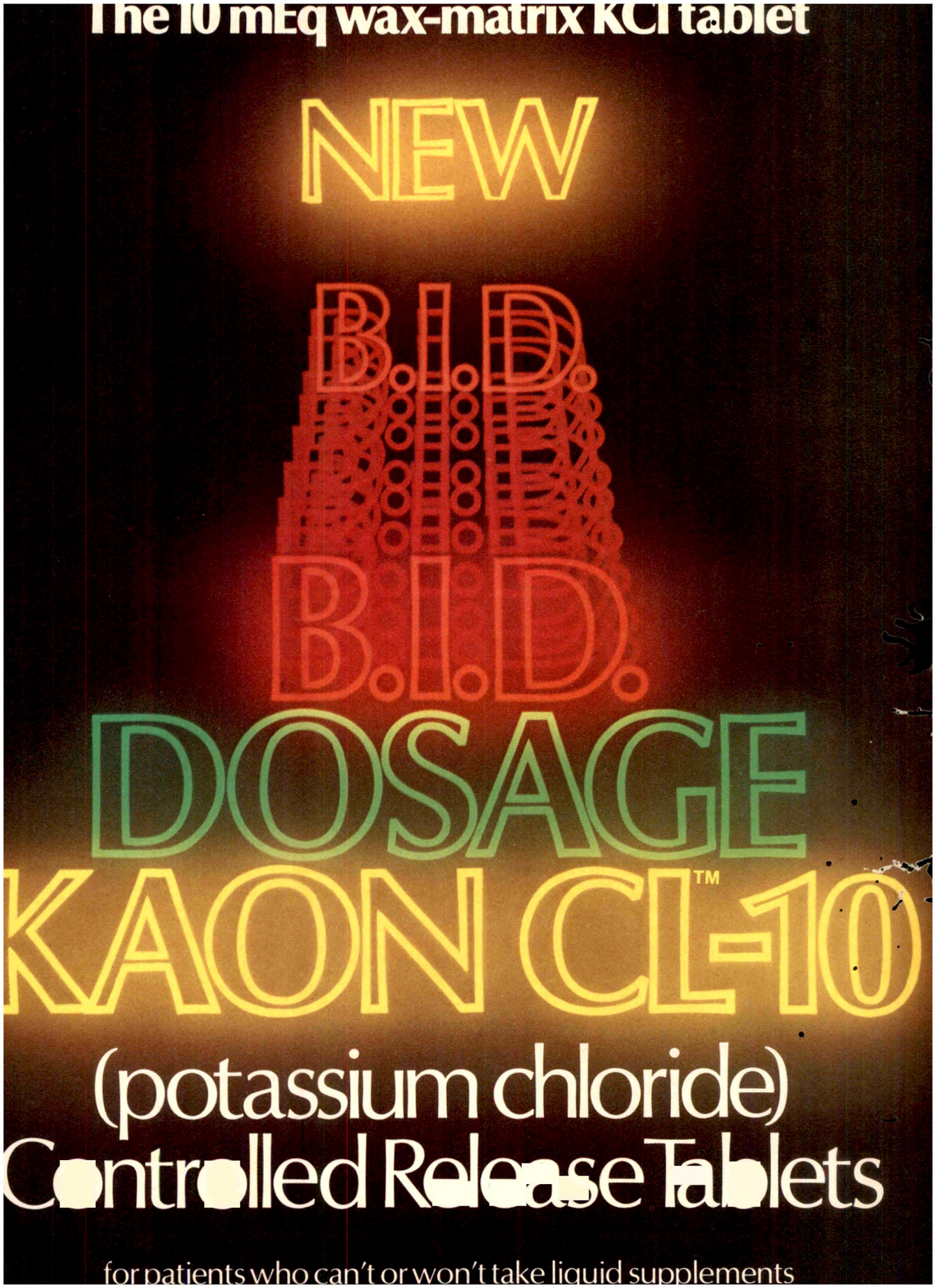
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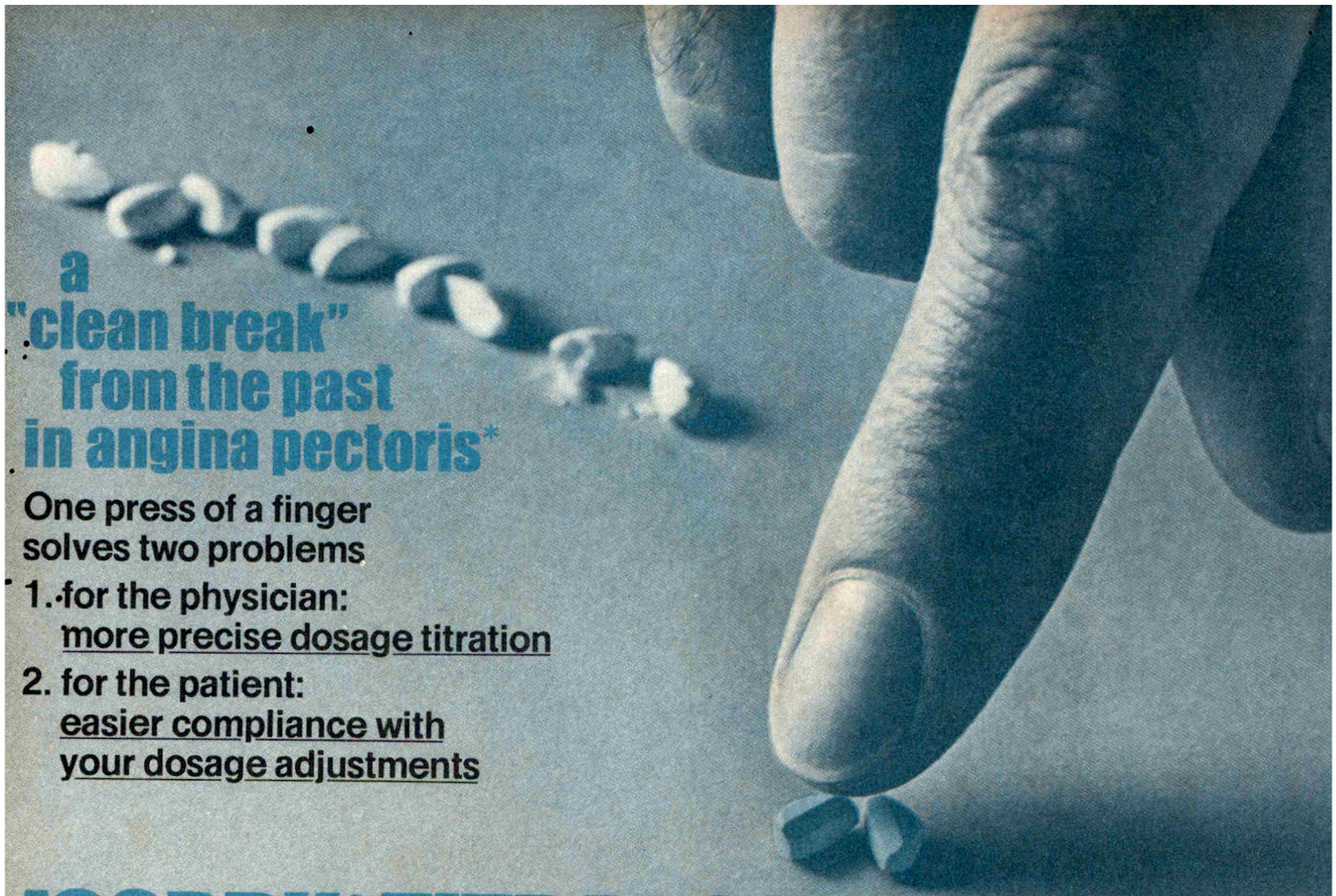

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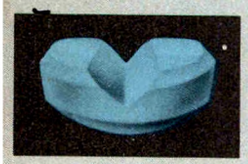

Tablet shown larger than actual size.

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***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
"Possibly" effective: When taken by the oral route, Isordil is indicated for the relief of angina pectoris (pain of coronary artery disease). It is not intended to abort the acute anginal episode, but is widely regarded as useful in the prophylactic treatment of angina pectoris.
Final classification of the less-than-effective indications requires further investigation.

Contraindication: Idiosyncrasy to this drug.

Warnings: Data supporting the use of nitrites and nitrates during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

Precautions: Tolerance to this drug and cross-tolerance to other nitrites and nitrates may occur.

Adverse Reactions: Cutaneous vasodilation with flushing. Headache is common and may be severe and persistent. Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop. This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents. An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

Dosage and Administration: Isordil (Isosorbide Dinitrate) Oral Titradose Tablets are administered orally. The dosage range is 5 mg to 30 mg q.i.d., with the usual dosage being 10 mg to 20 mg q.i.d.

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Improved Exercise Performance in Persons With Stable Angina Pectoris Receiving Diltiazem

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The effects of diltiazem, a calcium antagonist drug, were compared with those of placebo on exercise performance during a series of symptom-limited upright exercise tests. Ten patients with chronic stable angina were studied over a period of 7 weeks. The drug was administered in a random double-blind fashion and was evaluated at increasing dose levels of 120, 180 and 240 mg/day. Diltiazem was effective in increasing the total duration of exercise ($p < 0.001$) and the time to the first onset of angina ($p < 0.02$) and to the first appearance of 1 mm of S-T depression ($p < 0.02$). These effects were most marked at the highest dose level of diltiazem. The heart rate was reduced at rest ($p < 0.05$) and during submaximal exercise ($p < 0.001$). There was a reduction in diastolic blood pressure during submaximal exercise ($p < 0.04$) but no change in systolic pressure. Pressure-rate product was significantly reduced at submaximal ($p < 0.001$) but not maximal exercise. The reduction in pressure-rate product is postulated as the mechanism by which diltiazem enhances duration of exercise. There was no reduction in electrocardiographic evidence of myocardial ischemia at peak exercise by either clinical observation or computer analysis of spatial electrocardiographic variables. Five of the six patients who continued to take the drug maintained or improved their exercise performance on follow-up study 8 to 10 months later.

Specific pharmacologic agents[1] are now available that inhibit the influx of calcium ions during cell depolarization of both smooth and cardiac muscle. The partial inhibition of calcium passage into smooth muscle cells causes them to contract less vigorously. The theoretic possibility then arises that such drugs may be efficacious in the treatment of angina pectoris. Mechanisms for their effectiveness include dilatation of coronary arteries, with a resulting increase in coronary blood flow and reduced blood pressure, causing decreased myocardial oxygen demand during exertion. If calcium antagonists prove effective in the treatment of angina pectoris, they may be of special benefit to persons who also manifest varying degrees of airway obstruction and are unable to tolerate beta receptor blocking agents. Verapamil[2–4] and nifedipine,[5,6] two other "calcium antagonists," are reported to improve the symptomatic status of persons with angina pectoris. Diltiazem (d-3-acetoxy-cis-2,3-dihydro-5-[2-(diphenyl amino)-ethyl]-2(p-methoxyphenyl) 1,5-benzothiazepine-4(5H)-one hydrochloride) is another calcium antagonist; several studies[7–10] document the effectiveness of this drug in controlling symptoms of coronary arterial spasm.

There are few reports concerning the effectiveness of diltiazem in the treatment of angina pectoris caused by fixed stenoses in coronary arteries. This study describes the results of a double-blind study of diltiazem versus placebo in patients with angina pectoris whose responses to symptom-limited exercise testing were used to assess the effects of the drug.

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Methods

Study patients: Nine men and one woman were studied. The requirements for inclusion in the study were typical angina pectoris occurring 5 to 15 times/week, angina during exercise testing and 1 mm or more of horizontal or downsloping S-T depression during exercise testing. No patient was considered clinically to have coronary arterial spasm because none had chest pain at rest or nocturnal angina. Testing of response to ergonovine maleate or to sublingual nitroglycerin was not performed at cardiac catheterization. Patients with unstable angina, recent myocardial infarction (within 6 months) or significant noncardiac diseases were excluded. The physical characteristics, arteriographic findings and medical therapy of the patients before entry into the study are shown in Table I. Five patients were regular participants in a supervised exercise program. Each patient signed an informed consent form approved by the Human Subjects Committee at the University of Washington. None received monetary inducements to participate in the study. During the study, no patient changed his dietary pattern or lost weight. Four patients who smoked continued to do so in the same amount throughout the study. None undertook additional exercise during the study.

Exercise testing: Exercise tests were carried out using a treadmill. Speed and elevation were increased every 3 minutes. The initial speed was 1.7 miles/hour at a 5 percent gradient (stage 1/2) and, when that stage was completed, the test continued using the conventional stages of the Bruce protocol.[11] Subjects performed the test at approximately the same time of day each week and smoking was not permitted for 3 hours before testing. Subjects exercised to symptom-limited end points each time and neither S-T depression nor target heart rate was used as an indication for stopping the test. Heart rate and blood pressure were recorded with the patient seated at rest and then during each stage of the exercise test. The time in seconds from the start of testing to the first awareness of angina was recorded and the total duration of exercise noted. During exercise, the electrocardiogram was monitored using a modified V_5 lead (right scapula, V_5 position). The time from the start of exercise to 1 mm of horizontal or downsloping S-T depression was noted. Frank XYZ lead system signals were recorded on magnetic tape for subsequent computer analysis as previously described.[12]

Drug protocol: Diltiazem was supplied in 30 mg tablets and placebo tablets of identical appearance were also provided. Patients taking beta receptor blocking agents were withdrawn from therapy by incremental reductions in the dosage over a 4 day period. During the 1st week of the study, all patients received placebo, one tablet four times daily. After the 1st week, patients received either placebo or diltiazem in a double-blind random fashion. Three dose levels of diltiazem (120, 180 and 240 mg/day) were evaluated. The number of tablets/day was increased at 2 week intervals. Diltiazem was given in four divided doses during the 1st and final 2 week periods and in three divided doses for the mid 2 week period. Drug compliance was assessed by tablet count in returned bottles. During the study, patients used sublingual nitroglycerin but all other cardioactive drugs were discontinued. Use of nitroglycerin was not permitted immediately before exercise testing.

Patient evaluation: Before entry into the study, the patients performed an exercise test while receiving the medications listed in Table I. Exercise tests were repeated at weekly intervals so that each patient performed a total of eight exercise tests. A urinalysis, hematologic screen and biochemical profile were performed before the 1st week of placebo therapy and then at the end of the 4th and 7th weeks of the study. Each week, patients were questioned regarding possible adverse effects from the tablets.

Statistical analysis: The test results from this double-blind study were analyzed using an analysis of variance (ANOVA) routine from the statistical computing package, SPSS. This routine is capable of handling the repeated measurements made on each patient (for placebo and drug). Because the study was designed to compare diltiazem with placebo and because the patients were taking a variety of medications before the study, the results of the exercise test performed before the study were not included for statistical analysis but are shown for comparison. Comparisons between diltiazem and placebo at the three dose levels were also made using Student's paired t test.

Results

Duration of exercise: The mean and standard error of the mean of exercise duration for the tests are shown in Figure 1. Analysis of variance showed a significant increase in exercise duration while subjects were receiving diltiazem (F 5.1, $p < 0.001$). The difference in

TABLE I

Characteristics of Patients

Case	Age (yr) & Sex	Height (cm)	Weight (kg)	Diagnosis*	ECG	Arteriography†	Drug Treatment Before Study
1	45M	180	88	AP,DMI	N	. . .	Propranolol, 160 mg/day
2	63M	182	100	AP	N	. . .	Propranolol, 160 mg/day
3	63M	172	69	AP	N	90% LAD, 100% LCx, 90% RCA	Metoprolol, 400 mg/day; isosorbide dinitrate, 40 mg/day
4	73M	175	73	AP	N	75% septal	Propranolol, 120 mg/day
5	58M	170	77	AP	N	75% LAD, 90% LCx	Metoprolol, 150 mg/day
6	60M	165	74	AP,DMI	N	. . .	Nitroglycerin, sublingual
7	56M	177	102	AP,DMI	N	100% RCA	Isosorbide dinitrate, 40 mg/day
8	47M	164	69	AP,DMI	N	100% LCx, 100% RCA	Propranolol, 240 mg/day; isosorbide dinitrate, 40 mg/day
9	59M	169	72	AP	DMI	. . .	Propranolol, 120 mg/day
10	53F	161	58	AP, prior surgery‡	N	90% LAD, 100% LCx, 100% RCA	Propranolol, 80 mg/day; nitroglycerin ointment

* Diagnosis based on history and prior electrocardiogram. † % refers to cross-sectional area loss. ‡ Circumflex system was not grafted because of severe distal disease.

AP = angina pectoris; DMI = diaphragmatic myocardial infarct; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; N = normal; RCA = right coronary artery.

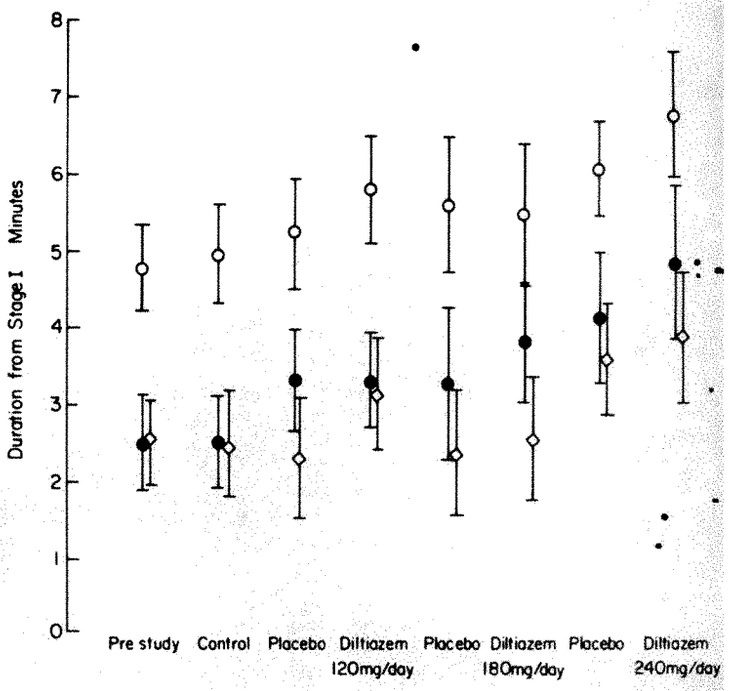

FIGURE 1. The duration in minutes from the beginning of stage I of the Bruce treadmill exercise protocol to the termination of exercise (**open circles**), from the start of stage I to the first onset of angina (**closed circles**) and from the start of stage I to the presence of 1 mm of horizontal or downsloping S-T depression (**open diamonds**) is indicated for each week of the study. Mean values ± standard error of the mean are shown. The prestudy value is shown but not included in the statistical analysis. Analysis of variance revealed a significant increase in the duration of exercise ($p < 0.001$), the time to onset of angina ($p < 0.02$) and the time to 1 mm of S-T depression ($p < 0.02$).

duration at the dose level of 240 mg/day of diltiazem was significant ($p < 0.01$) when compared with that in the corresponding week with placebo. When duration with 120 mg/day of diltiazem was compared with that in the corresponding week with placebo, the p value was not quite significant ($p = 0.056$). Surprisingly, there was no difference in duration at the level of 180 mg/day, and the possibility of subtherapeutic levels of diltiazem due to a prolonged interval between the last dose of the drug and exercise testing was considered. The mean interval from the last dose of diltiazem to exercise testing was 3.6 ± 1.7, 3.3 ± 1.3 and 3.3 ± 1.2 hours for the 120, 180 and 240 mg/day dose levels, respectively. However, three patients whose exercise duration was poorer at the 180 mg dose level had taken the drug at least 4 1/2 hours before testing. A prior study[13] reported that the maximal hemodynamic effect of diltiazem was observed 2 to 3 hours after administration of a single oral dose. Thus it is possible that the failure to observe a difference at the 180 mg/day dose level represents inadequate blood levels at the time of testing in some persons.

Time to first onset of angina: The mean and standard error of the mean of the interval from start of exercise to the first reported awareness of angina are shown in Figure 1. Analysis of variance showed a significant increase in the time to onset of angina while subjects were receiving diltiazem ($F 2.7$, $p < 0.02$). In general, the increase in exercise duration was accompanied by a corresponding increase in the time to first onset of angina. This was true for tests performed during placebo and diltiazem therapy. Table II shows the frequency of exercise-induced angina and exercise limiting angina. Although the frequency of angina decreased slightly while the patients were taking diltiazem, the differences were not significant.

Cardiovascular effects: The observed cardiovascular variables at rest and during exertion are presented in Table III. Overall, the heart rate at rest was reduced with diltiazem ($F 2.3$, $p < 0.05$). Paired t testing showed that the reduction of heart rate at rest at the 180 mg/day dose level was significant ($p < 0.05$). The reduction at 240 mg/day did not reach statistical significance when

TABLE II

Frequency of Angina During Exercise in 10 Patients

	Pre-study	Control	Placebo	Diltiazem (120 mg/day)	Placebo	Diltiazem (180 mg/day)	Placebo	Diltiazem (240 mg/day)
Patients with angina during exercise test (n)	10	10	10	10	10	9	10	8
Patients limited by angina during exercise test (n)	8	8	8	6	7	5	7	5

TABLE III

Cardiovascular Variables at Rest and Submaximal and Maximal Exertion

	Prestudy	Control	Placebo	Diltiazem (120 mg/day)	Placebo	Diltiazem (180 mg/day)	Placebo	Diltiazem (240 mg/day)	F Value*	p
Heart rate (beats/min)										
Rest	61 ± 10	72 ± 10	74 ± 9	72 ± 10	73 ± 11	69 ± 8†	74 ± 13	67 ± 7	2.3	0.05
Submaximal exercise	86 ± 11	97 ± 11	95 ± 12	91 ± 11	96 ± 11	92 ± 9	90 ± 11	84 ± 7†	7.9	0.001
Maximal exercise	112 ± 19	132 ± 14	134 ± 22	133 ± 18	132 ± 18	126 ± 22†	132 ± 18	133 ± 25	1.5	0.2
Systolic blood pressure (mm Hg)										
Rest	116 ± 13	177 ± 16	111 ± 8	114 ± 14	108 ± 13	111 ± 10	114 ± 10	111 ± 14	1.0	0.46
Submaximal exercise	127 ± 16	128 ± 15	133 ± 12	128 ± 11	127 ± 11	125 ± 12	128 ± 10	127 ± 14	0.9	0.53
Maximal exercise	141 ± 19	145 ± 20	147 ± 8	149 ± 15	150 ± 16	147 ± 19	149 ± 13	146 ± 17	0.2	0.96
Diastolic blood pressure (mm Hg)										
Rest	69 ± 8	72 ± 7	71 ± 6	72 ± 5	69 ± 7	69 ± 8	73 ± 7	68 ± 10†	1.3	0.26
Submaximal exercise	72 ± 6	75 ± 7	72 ± 6	72 ± 7	72 ± 5	71 ± 6	76 ± 8	69 ± 7†	2.4	0.04
Maximal exercise	71 ± 7	74 ± 6	73 ± 6	75 ± 5	73 ± 6	72 ± 5	76 ± 6	69 ± 6‡	2.1	0.06
Pressure-rate product × 10^{-2}										
Rest	69 ± 15	84 ± 19	83 ± 13	81 ± 19	79 ± 17	76 ± 10	84 ± 20	76 ± 11	1.9	0.09
Submaximal exercise	109 ± 21	123 ± 20	126 ± 20	117 ± 21	122 ± 18	114 ± 17	116 ± 21	107 ± 16†	4.0	0.001
Maximal exercise	158 ± 35	193 ± 36	198 ± 32	200 ± 40	197 ± 43	186 ± 48	198 ± 36	196 ± 47	0.5	0.79

* F value obtained from analysis of variance of values obtained while patients were receiving placebo and diltiazem. †,‡ Probability results of paired *t* test comparing results of diltiazem exercise test with corresponding placebo exercise test: † $p < 0.05$; ‡ $p < 0.005$.
p = probability.

compared with the corresponding placebo period although the mean difference was greater than for the 180 mg/day period. The most significant reduction in heart rate (F 7.9, $p < 0.001$) occurred during submaximal exercise. There was a definite increase in the magnitude of reduction with increasing dosage of diltiazem. At maximal exercise, there was no significant change in maximal heart rate although paired *t* testing showed that the mean value for the 180 mg/day period was significantly lower ($p < 0.05$) than the value for the corresponding placebo period. The reason for this finding is not clear and may indicate patient variability or possible failure of several persons to perform maximal exertion.

There were no significant reductions in systolic blood pressure at rest or during exercise. Diastolic blood pressure was significantly reduced at submaximal and maximal exercise. These reductions were most marked when diltiazem was given in a dosage of 240 mg/day.

Pressure-rate product was not significantly changed at rest. There was a highly significant (F 4.0, $p < 0.001$) reduction in submaximal pressure-rate product associated with diltiazem. At maximal exercise pressure-rate product was not significantly reduced.

Electrocardiographic effects: Table IV presents the effects of diltiazem on the electrocardiographic evidence of myocardial ischemia. There was no significant reduction in either the visual reading of S-T depression or the computer measured indexes of myocardial ischemia. Figure 1 shows the time from the commencement of exercise until the appearance of 1 mm of horizontal or downsloping S-T depression. Diltiazem delayed the onset of this electrocardiographic evidence of myocardial ischemia ($p < 0.02$).

Adverse effects: No significant changes in the urinalysis, hematologic or biochemical profiles were observed. One patient reported headaches on two occasions, once while taking diltiazem and once while taking placebo. An additional patient not reported on in Table I who had angina and an occluded right coronary artery

TABLE IV

Electrocardiographic Evidence of Ischemia at Rest, Submaximal and Maximal Exertion

	Prestudy	Control	Placebo	Diltiazem (120 mg/day)	Placebo	Diltiazem (180 mg/day)	Placebo	Diltiazem (240 mg/day)	p
S-T depression V_5 (mv)									
Rest	0	0	0	0	0	0	0	0	NS
Submaximal exercise	0.2 ± 0.6	0.3 ± 0.6	0.3 ± 0.6	0.3 ± 0.9	0.3 ± 0.6	0.1 ± 0.3	0.1 ± 0.3	0.3 ± 0.6	NS
Maximal exercise	2.4 ± 1.6	2.2 ± 1.5	2.7 ± 1.9	2.5 ± 1.7	2.8 ± 2.2	2.5 ± 2.0	2.7 ± 2.1	2.6 ± 2.3	NS
MS · Θ (mV degrees)*									
Rest	—	3.8 ± 3.8	2.1 ± 1.1	3.6 ± 5.2	2.2 ± 2.9	2.7 ± 3.5	2.4 ± 2.6	2.6 ± 4.2	NS
Submaximal exercise	—	1.7 ± 1.6	2.9 ± 2.4	4.6 ± 6.4	2.8 ± 3.8	3.3 ± 6.3	1.6 ± 1.3	3.2 ± 2.6	NS
Maximal exercise	—	21.5 ± 9.1	21.4 ± 9.8	18.9 ± 10.9	20.1 ± 12.1	20.4 ± 10.4	18.9 ± 10.6	17.5 ± 13.4	NS
MST_{75} · Θ (mV degrees)*									
Rest	—	6.7 ± 6.1	4.6 ± 3.3	7.1 ± 9.8	3.2 ± 1.3	3.7 ± 3.3	3.4 ± 3.0	4.8 ± 5.4	NS
Submaximal exercise	—	3.7 ± 4.4	5.9 ± 4.1	5.4 ± 5.5	3.3 ± 4.2	6.1 ± 8.9	3.5 ± 3.7	4.4 ± 3.1	NS
Maximal exercise	—	20.0 ± 11.4	22.8 ± 12.2	21.7 ± 12.1	20.7 ± 13.7	19.4 ± 11.7	18.4 ± 11.7	17.4 ± 14.6	NS

* MS · Θ and MST_{75} · Θ are measurements of myocardial ischemia derived from analysis of Frank XYZ leads.
NS = not significant; p = probability.

TABLE V

Comparison of Control and Long-Term Cardiovascular and Electrocardiographic Variables in Six Patients

	Control		Diltiazem		
	Mean	SD	Mean	SD	p
Exercise duration (s)	300	± 109	471	± 224	<0.05
Maximal oxygen uptake (ml/min per kg)	19.85	± 4.16	25.12	± 8.27	<0.05
Heart rate (beats/min)					
Rest	74	± 9	67	± 7	<0.05
Submaximal exercise	113	± 18	98	± 14	<0.01
Maximal exercise	136	± 18	138	± 26	NS
Systolic blood pressure (mm Hg)					
Rest	112	± 12	109	± 18	NS
Submaximal exercise	142	± 11	130	± 20	NS
Maximal exercise	142	± 12	158	± 11	<0.05
Diastolic blood pressure (mm Hg)					
Rest	72	± 10	63	± 7	<0.05
Submaximal exercise	77	± 8	73	± 7	NS
Maximal exercise	75	± 9	75	± 10	NS
Pressure-rate product × 10^{-2}					
Rest	83	± 17	73	± 14	<0.05
Submaximal exercise	160	± 33	128	± 31	<0.01
Maximal exercise	193	± 34	219	± 49	NS
S-T depression V_5 (mV)					
Rest	0		0		NS
Submaximal exercise	1.0	± 1.1	0.3	± 0.8	0.05
Maximal exercise	3.3	± 1.9	2.3	± 1.7	NS

NS = not significant; p = probability value (paired *t* test); SD = standard deviation.

withdrew from the study during the 2nd week because of depression. He was receiving placebo.

Follow-up: At the end of the study all patients were given an opportunity to participate in a long-term study. Six of the patients agreed to do so and they have now been followed up for 8 to 10 months. The remaining four declined; two (Cases 2 and 4) recommenced propranolol therapy and the other two (Cases 6 and 7) are taking long-acting nitrates. Of the six who entered the long-term study, one (Case 3) underwent successful aorto-coronary vein bypass grafting after 4 months; the other five continue to take diltiazem (240 or 360 mg/day). The results of exercise testing, including measurement of maximal oxygen uptake, are shown in Table V. Included in this table are control values for comparison. The five patients who are currently taking the drug showed significant improvement with a measured increase in maximal oxygen uptake as well as enhanced duration of exercise. Changes in heart rate and pressure-rate product with long-term usage of diltiazem are consistent with the findings in the short-term study.

Discussion

Beneficial effects of diltiazem in angina pectoris: The results of this study are encouraging because they indicate that diltiazem, in a dosage of 240 mg/day, was associated with an increased duration of exercise, prolonged the time to onset of angina and eliminated angina as the symptom for limiting exercise in some cases. When the duration of exercise during the treatment period of 240 mg/day of diltiazem was compared with the exercise test performed immediately before the study, all patients showed an increase ($p < 0.005$) and nine experienced an increase in duration to the onset of angina ($p < 0.05$).

The heart rate and blood pressure responses to exercise observed in this study provide some insight into the possible mechanism by which diltiazem and possibly calcium antagonists in general exert a beneficial effect. It appears that heart rate is reduced at rest and at submaximal exertion, but there was no significant change in maximal heart rate during exercise.

Comparisons with nifedipine and verapamil: Moskowitz et al.[6] found that nifedipine, another calcium antagonist, did not alter heart rate at rest, but Eklund and Oro[5] reported a significant increase in heart rate with nifedipine during upright bicycle exercise. In a report[3] of the effects of verapamil, maximal heart rate was reduced but two other studies[2,4] recorded no change in heart rate. The mechanisms for the heart rate responses are not clear but a possible explanation for the increased heart rate response with nifedipine is a reflex tachycardia associated with afterload reduction because systolic blood pressure was significantly reduced at rest and at submaximal and maximal exercise. In contrast, verapamil was reported to cause no change in heart rate despite a reduction in systolic blood pressure in one study,[4] and in another[3] heart rate was reduced without a change in systolic pressure. Similarly, the results of our study with diltiazem show reductions in heart rate without changes in systolic blood pressure at submaximal exertion. Kinoshita et al.,[14] using a single oral dose of 60 mg of diltiazem, found reductions in heart rate at rest and systolic blood pressure but no change in values during supine bicycle exercise. It is possible that verapamil and diltiazem may depress sinoatrial nodal automaticity as a result of calcium blockade to account for the heart rate responses. Verapamil prolongs atrioventricular conduction whereas nifedipine does not have such an effect in human beings.[15] It is apparent there are electrophysiologic differences among the various calcium antagonists and there may well be varying he-

modynamic differences. A consistent finding confirmed by this study and reported for nifedipine,[6] verapamil[2,4] and diltiazem[14] was the decrease in diastolic pressure suggesting that there was a decrease in peripheral resistance.

Effect on electrocardiographic evidence of ischemia: Our study failed to show any reduction in electrocardiographic evidence of myocardial ischemia at peak exercise. Too few patients experienced a significant amount of S-T depression during stage 1/2 and stage 1 to evaluate the effect of diltiazem on myocardial ischemia at submaximal exercise levels. However, the time to onset of 1 mm of S-T depression was significantly prolonged with diltiazem, suggesting that diltiazem does reduce electrocardiographic evidence of ischemia. Results of studies with verapamil[2,3] and nifedipine[6] suggested that these drugs decrease the magnitude of electrocardiographic evidence of myocardial ischemia during exercise. The reduction in pressure-rate product is indirect evidence of decreased myocardial oxygen demand.[16]

Dosage schedule: The dosage of diltiazem chosen for this study was based on Japanese data,[7–10,14] which showed impressive symptomatic and hemodynamic changes with small doses (total 90 mg/day). In prescribing diltiazem, an initial dosage of 240 mg/day would appear to be appropriate and further studies evaluating the effect of 360 mg/day are in progress. Because more consistent findings were found with a schedule of four rather than three times daily, the former is preferred.

Possible limitations of study: This study design imposes some limitations on the interpretations of the results. There was a nonspecific increase in exercise duration as the study progressed (Fig. 1). This was partly due to the increasing familiarity of the patients with the equipment and exercise protocol; however, all subjects had prior experience of treadmill testing on several occasions. It was unlikely that a training effect occurred and certainly there was no hemodynamic changes to support a training effect (that is, no significant change in submaximal pressure-rate product for the weeks of placebo therapy). When the control values were compared with those of the last week of placebo therapy and the last week of diltiazem therapy, the change was greater with diltiazem ($p < 0.005$) than with placebo ($p < 0.005$). Similarly, the time to onset of angina increased more with diltiazem ($p < 0.02$) than with placebo ($p < 0.05$). However, the statistical analysis using analysis of variance gives a more meaningful assessment of the significance of changes associated with diltiazem.

The long-term follow-up data on the six patients who continued to receive diltiazem were consistent with a beneficial effect of the drug. The small number of patients studied imposed limitations on the study and may have been responsible for some of the variation seen in the maximal heart rate at the dosage of 180 mg/day of diltiazem. A study comparing the effects of diltiazem with standardized conventional therapy in persons with angina over a long period of time would provide an additional assessment of the efficacy of diltiazem. Another aspect that should be evaluated in such a study is the possible difference between calcium antagonists and beta receptor blocking agents with regard to causing fatigue. In our study, six of the eight patients who were taking beta blocking agents before testing noted a loss of fatigue when these agents were discontinued during the study. Several also noted that their ability to perform cognitive duties was greater during the study period than during periods of propranolol usage.

Clinical implications: Diltiazem is an effective drug in the symptomatic treatment of exercise-induced angina pectoris. Undoubtedly, the relative contributions of coronary arterial spasm and fixed arterial obstructions to the pathophysiology of angina vary among patients. Some in whom spasm is the dominant factor may derive the greatest symptomatic benefit from diltiazem and similar compounds. In this study, no patient had clinical evidence of coronary spasm and all manifested improved exercise performance over the prestudy test results while receiving the highest dosage of diltiazem, thus suggesting that this drug is effective even in the presence of fixed coronary artery disease. In the dosages used and in the short period of time studied, diltiazem had remarkably few adverse effects. Because diltiazem may facilitate the adaptive responses to physical training, compliance and adherence to a training schedule may be enhanced. A recent report indicated that patients taking verapamil after myocardial infarction were able to participate successfully in an exercise program.[17] In contrast, serious doubts have been raised concerning the ability of patients receiving propranolol to obtain a significant training effect.[18,19] The occasional clinical problem of a patient with reversible airway obstruction and angina may be an additional indication for treatment with diltiazem.

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Effect of Intravenous and Intracoronary Nitroglycerin on Left Ventricular Wall Motion and Perfusion in Patients With Coronary Artery Disease

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Left ventricular anterior wall motion and distribution of coronary perfusion were assessed by contrast cineangiography and the dual isotope-labeled intracoronary microsphere technique before and after intravenous or intracoronary administration of nitroglycerin in 30 patients with significant left anterior descending coronary artery disease and resting anterior wall asynergy. Perfusion was measured in 11 additional control patients before and after administration of saline solution. Reversible asynergy was observed in 6 (43 percent) of 14 patients after systemic (intravenous) nitroglycerin and in 7 (44 percent) of 16 patients after intracoronary nitroglycerin. Significant reductions of blood pressure and improved wall motion were noted in both groups receiving nitroglycerin, suggesting afterload reduction as the common mechanism. There was also a small increase in end-diastolic volume index in patients with reversible asynergy after intracoronary administration of nitroglycerin, but no significant trends in preload change after intravenous administration. Ejection fraction increased significantly in patients with reversible asynergy after both intravenous and intracoronary nitroglycerin. Both intravenous and intracoronary nitroglycerin resulted in significant increases and decreases in distribution of coronary perfusion to the anterior wall. However, these changes were randomly distributed and improved perfusion did not consistently occur with improved wall motion.

In conclusion, both intravenous and intracoronary nitroglycerin may reverse wall motion asynergy and produce both favorable and unfavorable changes in perfusion in patients with coronary disease. The common mechanism in improving wall motion with either intravenous or intracoronary nitroglycerin was afterload reduction, suggesting that the systemic effects of nitroglycerin are the most important in reversing asynergy.

Nitroglycerin has been used at the time of left ventricular angiography to improve wall motion of impaired segments of the left ventricle in patients with coronary artery disease.[1–4] Nitroglycerin could have a beneficial effect on impaired wall motion through various mechanisms, including its systemic effect on preload and afterload,[5–8] redistribution of coronary flow to ischemic segments[9,10] or possibly a direct myocardial effect.[11] Previous clinical studies have produced conflicting results, particularly in respect to alterations in coronary flow and its distribution[9,10,12,13] and have not discriminated among the relative contributions of these effects. To determine the mechanism of action of nitroglycerin on wall motion, we studied the effects of both systemic and intracoronary nitroglycerin on wall motion and distribution of coronary flow in patients with coronary disease.

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Methods

Study patients: Forty-one patients undergoing cardiac catheterization with selective coronary arteriography were studied. There were 37 men and 4 women, with a mean age of 49.6 years (range 32 to 64). Thirty patients had triple vessel coronary artery disease, six had double vessel disease, three had single vessel disease and two had normal coronary arteries. All patients receiving nitroglycerin had 75 percent or greater stenosis of the diameter of the left anterior descending artery and resting anterior wall motion abnormalities. In all but one patient the stenosis of the left anterior descending artery was at or proximal to the first septal perforator. Of the 11 control patients, 2 had normal coronary arteries and 9 had disease of the left anterior coronary descending artery. All patients except the two in the control group with normal coronary arteries had stable angina pectoris of grade II or III severity (New York Heart Association classification).[14] None had congestive heart failure and all had sinus rhythm. Thirteen of the study group receiving nitroglycerin had Q waves or no "R wave progression" in the precordial leads diagnostic of a previous anterior myocardial infarction. Eight patients had angiographically visualized collateral vessels to the left anterior descending coronary artery (see Results). In all patients administration of nitroglycerin and long-acting nitrates had been discontinued 24 hours or more before study. The dosage of propranolol was reduced to 80 mg/day or less before catheterization. In two patients receiving digoxin administration of the drug had been discontinued for at least 24 hours before the study. All patients gave signed, informed consent.

Protocol: After the patients were premedicated with 50 to 75 mg of Demerol® and 25 mg of Phenergan® intramuscularly, two catheters were inserted, one in each groin, by the percutaneous femoral technique. A pigtail catheter was placed in the left ventricle and a left Judkins catheter was placed just above the left coronary ostium. Baseline aortic pressures and heart rate were recorded. The left Judkins catheter was then placed in the ostium of the left coronary artery and its position verified by injection of a minimal amount (less than 0.5 cc) of Renografin-76®. Macroaggregated human serum albumin (0.5 to 0.8 ml.) labeled with 2 millicuries (mCi) of technetium-99m was selectively injected into the left coronary artery. Sixteen patients then received 0.06 mg of nitroglycerin into the left coronary artery and 14 received 0.4 mg of nitroglycerin intravenously. Eleven patients who served as a control group received an equal volume of saline solution. Macroaggregated human serum albumin (0.5 to 1.0 ml) labeled with 100 mCi. of iodine-131 was selectively injected into the left coronary artery when peak changes in pressure and heart rate were obtained in the patients receiving intravenous nitroglycerin or within 15 seconds in patients receiving intracoronary nitroglycerin and those in the control group.

A waiting period of 20 minutes was then allowed for dissipation of the effects of the previous administration of nitroglycerin with return of aortic pressure and heart rate to control levels. A left ventricular angiogram was then performed with 40 to 45 cc of Renografin-76 at an injection rate of 12 to 14 ml/s with the patient in the 30° right anterior oblique position. After a second rest period, nitroglycerin was again given by the same route and in the same dose as previously and a postnitroglycerin angiogram was performed using the same quantity and injection rate of dye as before. This angiogram was performed at precisely the same time after administration of nitroglycerin as described for injection of the second labeled macroaggregate. Selective coronary arteriograms were then performed by the Judkins technique in multiple views. There were no complications associated with the procedure.

Myocardial imaging techniques: After completion of the cardiac catheterization, myocardial imaging was performed on a Toshiba large field of view gamma camera with a dual nuclide adaptor using a high energy parallel hole collimator. Iodine-131 was peaked at 360 KeV with a 20 percent window and technetium-99m was peaked at 140 KeV with a 20 percent window. Patients were imaged in the 45° left anterior oblique position in order to separate accurately left anterior descending and circumflex arterial perfusion territory. Data were stored in a PDP 11/40 computer for subsequent analysis. Counts within irregular areas of interest corresponding to the distribution of perfusion of the left anterior descending artery were normalized by expressing them as a fraction of counts in the total myocardium. The ratio of counts before and after administration of nitroglycerin was calculated for that perfusion territory. The significance of changes in perfusion was determined by comparing count ratios before and after nitroglycerin in the study group with those in the control group using the unpaired Student's t test. Changes in the left anterior descending arterial distribution of perfusion after nitroglycerin were then compared with changes in anterior wall motion assessed angiographically.

Analysis of cineangiograms: End-diastolic and end-systolic silhouettes were drawn from contrast cineangiograms with a calibration mark included. These silhouettes were taken within the first 3 beats of the angiogram and were not preceded by a ventricular premature complex. Volumes were calculated using a computer-assisted modification of Simpson's rule[15] and ejection fraction was derived. The long axis from the mid aortic plane to the apex was quadrisected, and three perpendicular chords drawn to the anterior wall for the end-diastolic and end-systolic frames.[16] The percent of chordal shortening for the angiograms obtained before and after nitroglycerin was calculated and the average change of the three anterior wall chords used. The angiographic data obtained before and after nitroglycerin were compared using the paired Student's t test.

Results

Angiographic Analysis of Wall Motion

Analysis of anterior wall motion in the contrast angiograms showed the following responses to nitroglycerin. After intravenous nitroglycerin 6 of 14 patients demonstrated a greater than 5 percent increase in anterior wall percent chord shortening (Fig. 1A); the remaining 8 showed either no change or a decrease. After intracoronary nitroglycerin 7 of 16 patients showed a greater than 5 percent increase in anterior wall percent chord shortening; and 9 showed no change or a decrease (Fig. 1B). Intravenous nitroglycerin significantly reduced systolic blood pressure in patients with improved and unimproved anterior wall motion (Fig. 2). The mean (± standard error of the mean) decrease in systolic blood pressure was 31 ± 6 mm Hg for those with improved anterior wall motion and 19 ± 4 mm Hg for those with unimproved wall motion. There was no significant difference between these two mean values. Intracoronary nitroglycerin produced a much smaller but significant (7 ± 3 mm Hg) mean decrease in those with improved wall motion, and no significant trend in those with unimproved anterior wall motion. No significant trends were seen in changes in mean heart rate with intravenous nitroglycerin. However, there was a small but significant increase in mean heart rate from 58 ± 3 to

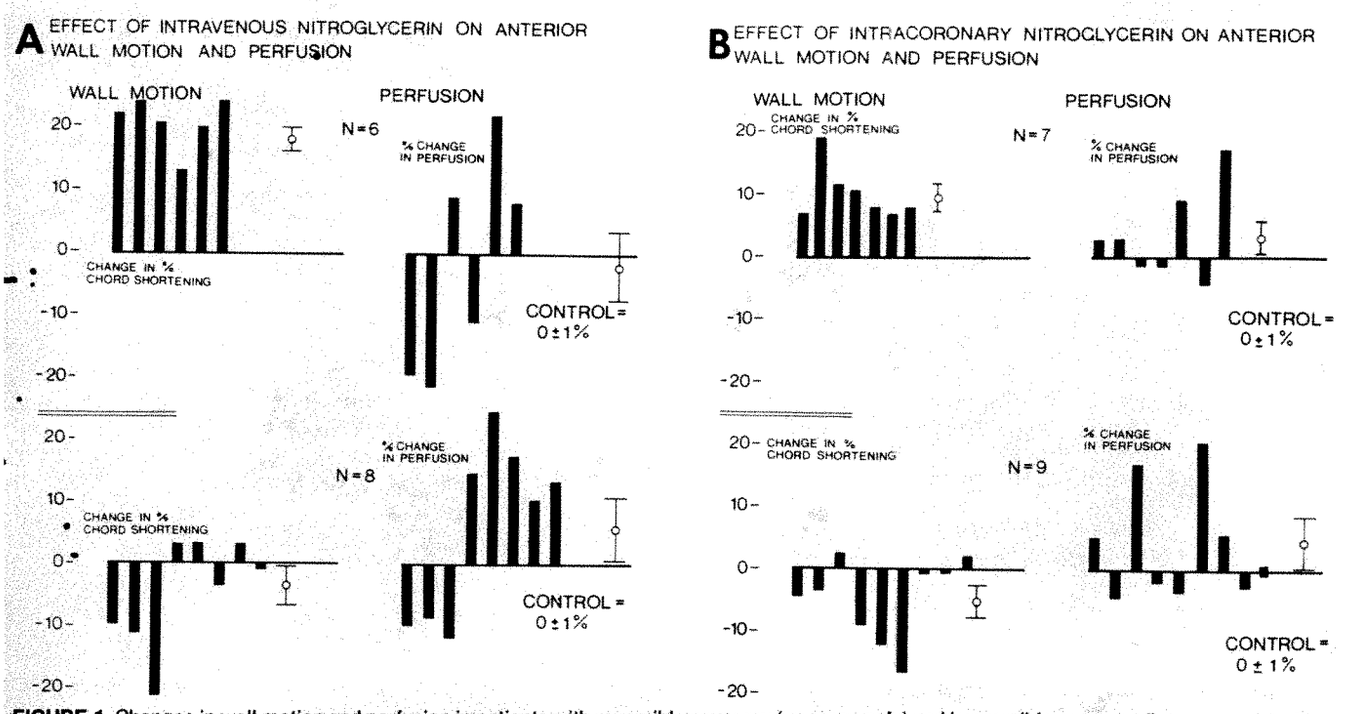

FIGURE 1. Changes in wall motion and perfusion in patients with reversible asynergy (**upper panels**) and irreversible asynergy (**lower panels**) after intravenous (A) and intracoronary (B) administration of nitroglycerin.

62 ± 2 beats/min with intracoronary nitroglycerin in those with improved anterior wall motion.

End-diastolic volume index (Fig. 3) significantly increased by a small amount in the group with improved anterior wall motion after intracoronary nitroglycerin, but no significant changes in this index occurred in the other groups. Global ventricular function as measured by ejection fraction (Fig. 4) improved significantly in those patients with improved wall motion after either intravenous or intracoronary nitroglycerin, but did not improve in patients with irreversible asynergy of the anterior wall.

Three of six patients with improved wall motion after intravenous nitroglycerin and three of the eight with unimproved wall motion had anterior Q waves in the electrocardiogram. In the group given intracoronary nitroglycerin one of the seven patients with improved wall motion and six of the remaining nine patients with unimproved wall motion had anterior Q waves.

Analysis of collateral circulation in the group receiving intravenous nitroglycerin revealed six patients with collateral circulation to the left anterior descending coronary artery, including four with improved wall motion and two with unimproved motion. In the group receiving intracoronary nitroglycerin, no patients with improved wall motion and two with unimproved motion had collateral circulation to the left anterior descending artery.

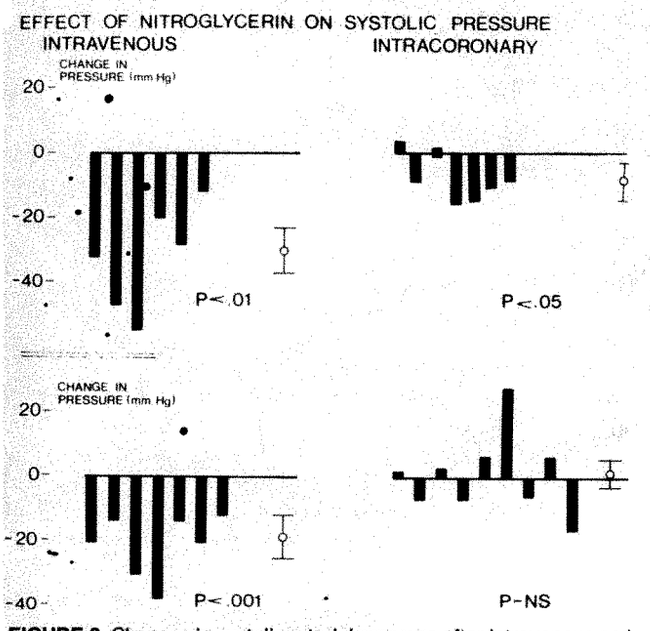

FIGURE 2. Changes in systolic arterial pressure after intravenous and intracoronary administration of nitroglycerin in patients with reversible asynergy (**upper panels**) and irreversible asynergy (**lower panels**).

Coronary Perfusion Analysis

To assess the variability of the dual isotope technique for measuring changes in the distribution of perfusion in a single coronary vessel after an intervention, 11 control patients were studied. The mean change (± standard error of the mean) in distribution of perfusion in the left anterior descending arterial territory measured by the two isotopes after saline solution alone was 0.0 ± 1.0 percent. The significance of changes in distribution of perfusion in patients receiving nitroglycerin

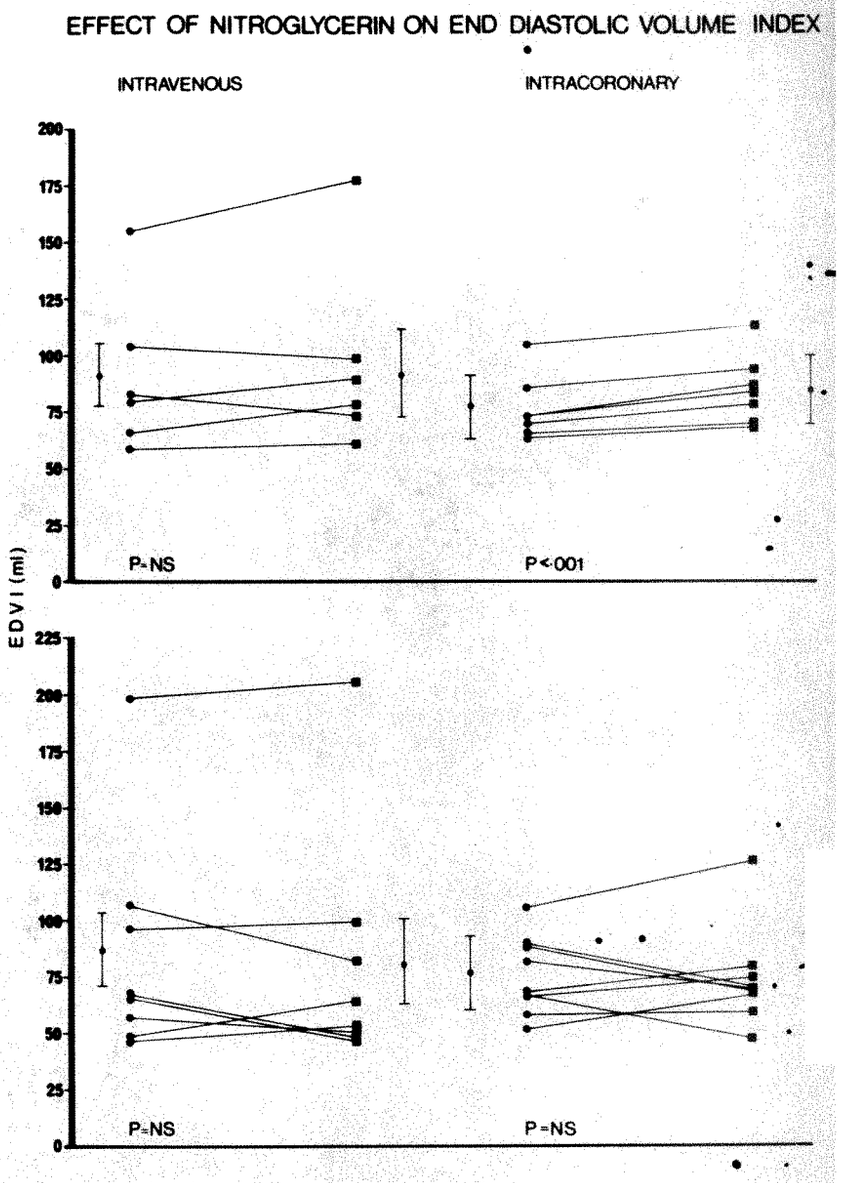

FIGURE 3. Changes in end-diastolic volume index (EDVI) after intravenous and intracoronary administration of nitroglycerin in patients with reversible asynergy (**upper panels**) and irreversible asynergy (**lower panels**).

was determined by comparison with this control value. In patients receiving intravenous nitroglycerin there were significant increases and decreases in distribution of perfusion in the territory of the left anterior descending coronary artery with both improved as well as unimproved wall motion. However, these changes were randomly distributed and did not correlate with wall motion changes (Fig. 1A). Similarly, in the patients receiving intracoronary nitroglycerin there were small but still significant increases and decreases in perfusion, but no correlation with changes in wall motion (Fig. 1B).

In order to determine the possible effect of changes in end-diastolic pressure on perfusion, these pressures were compared before and after intracoronary nitroglycerin in patients with improved perfusion and in those with no change or decreased distribution to the anterior wall. There were no significant differences in end-diastolic pressures before and after intracoronary nitroglycerin for either group (13.7 ± 4.8 versus 15.1 ± 5.8 mm Hg, p = NS, increased perfusion; 15.1 ± 10.1 versus 15.8 ± 9.4 mm Hg, p = NS, no change or decreased perfusion) (mean ± standard deviation).

Discussion

Effects of Nitroglycerin on Wall Motion

Mechanisms of improved ventricular wall motion: Nitroglycerin given at the time of left ventricular angiography has been shown to improve impaired left ventricular segmental wall motion in some patients with coronary artery disease.[1–4] Several mechanisms could contribute to this observed improvement. Nitroglycerin reduces afterload by decreasing systemic pressure which would directly enhance fiber shortening.[7,17] Its effect in reducing both preload and afterload would reduce oxygen requirements of an ischemic segment and could thereby improve its contractility.[5–8] Nitroglycerin could

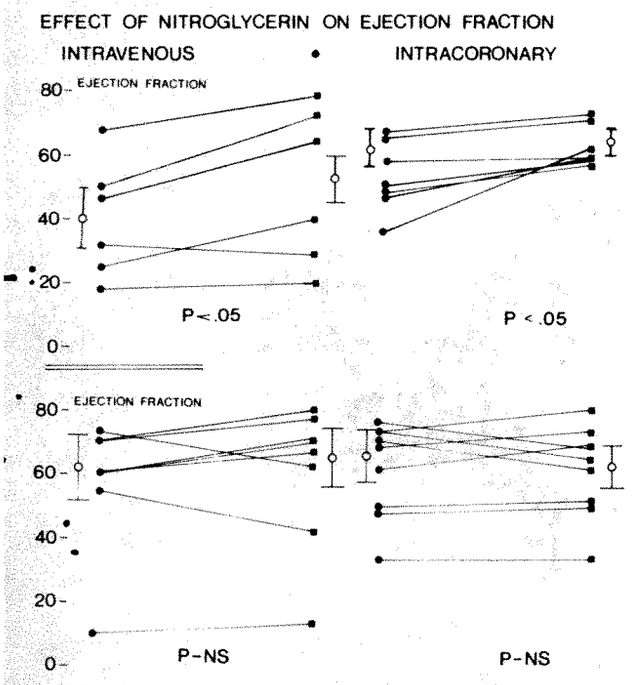

FIGURE 4. Changes in ejection fraction after intravenous and intracoronary administration of nitroglycerin in patients with reversible asynergy (**upper panels**) and irreversible asynergy (**lower panels**).

also induce a redistribution of perfusion to ischemic zones and improve oxygen supply.[9,10] Finally, a direct or indirect inotropic action has been suggested.[11] The operative mechanism was not investigated in these initial studies. Further studies have provided evidence for the link between reversible asynergy and reversible myocardial ischemia. Studies by Banka[18] and Bodenheimer[19] and their co-workers have shown that coronary arterial narrowing may produce resting reversible asynergy in zones of histopathologically normal myocardium. Our results concur with theirs in that the presence of Q waves was associated with unimproved wall motion after intracoronary nitroglycerin, although there was no such trend in the patients given intravenous nitroglycerin. More recent studies with thallium-201 myocardial scintigraphy[20,21] have shown that zones with reversible asynergy are associated with exercise-induced perfusion defects. Both experimental[22] and clinical[23] studies have shown an improvement in asynergy with reperfusion of zones supplied by a narrowed coronary artery.

All of these data suggest that asynergy reversible with nitroglycerin is the result of a favorable alteration of the myocardial supply-demand ratio in ischemic but anatomically normal myocardium. However, these studies have not determined if this reversibility results from a direct effect of nitroglycerin on distribution of flow or a reduction of myocardial oxygen demand or perhaps a combination of both. In our study we compared the effects of intravenous and intracoronary nitroglycerin to distinguish direct coronary from systemic effects. We also assessed the effects of systemic and intracoronary nitroglycerin on distribution of coronary flow to determine if changes in wall motion were related to changes in flow.

Effect on ventricular afterload: Systemic nitroglycerin, as expected, resulted in a decrease in systolic arterial pressure. In 43 percent of these patients anterior wall motion was improved after nitroglycerin (Fig. 1A). This improvement could be secondary to any of the previously mentioned factors, including both the effects of nitroglycerin on afterload and coronary perfusion. In the group receiving intracoronary nitroglycerin 44 percent of patients had improved anterior wall motion associated with a small but significant decrease in systolic pressure. The other 56 percent of patients had no improvement after intracoronary nitroglycerin and no significant change in blood pressure even though several had redistribution of perfusion to the anterior wall. This observation suggests that the improved wall motion could have been secondary, at least in part, to the effect of the nitroglycerin, after passing through the coronary circulation, reaching the systemic vascular bed and reducing blood pressure. These data in both the group receiving intracoronary and that receiving systemic nitroglycerin point to afterload reduction as a common factor improving wall motion.

Effect on preload: The other recognized systemic effect of nitroglycerin is on left ventricular preload. In this study, we observed a variable response, with both decreases and increases in end-diastolic volume. Of interest, there was a small but significant increase in end-diastolic volume in the seven patients with improved wall motion after intracoronary nitroglycerin. This raises the possibility of a small contribution from the Frank-Starling effect, along with the afterload effect, in augmenting wall motion in these patients. This increase in end-diastolic volume in some of the patients is less easily explained than the expected reduction in volume observed by other workers.[5,6] A direct effect of nitroglycerin in reducing left ventricular compliance is possible. Another possibility is a coronary steal effect altering perfusion and contraction outside the territory of the left anterior descending coronary artery, resulting in ventricular dilation. As discussed later, a coronary steal from the right coronary artery to the left anterior descending artery would not be measured by this technique. However, only one of these seven patients with increased end-diastolic volume had collateral vessels and these were from both the left anterior descending and left circumflex arteries to the right coronary artery. The other six patients had no collateral circulation, and thus would be unlikely to have an unmeasured "steal" effect. A more likely explanation would be a reduction in right ventricular volume allowing more complete left ventricular filling.[9,24]

Effects of Nitroglycerin on Coronary Perfusion

We utilized the dual isotopic techinique[25–27] in this study to assess the effect of both systemic and intracoronary nitroglycerin on coronary perfusion. By imaging in the left anterior oblique view after radionuclide injection into the left main coronary artery, the perfusion

territory of the left anterior descending artery, and hence of the anterior wall, can be isolated from circumflex arterial perfusion. To assess the reliability of the method, control patients received technetium-99m or iodine-131–labeled particles in random order before and after intracoronary injection of saline solution. Distribution of perfusion to the left anterior descending territory varied by 1 percent after saline injection. Comparison of the nitroglycerin groups with this control group reveals that both intracoronary and intravenous nitroglycerin resulted in significant changes in distribution of perfusion (Fig. 1). These changes were increased in some patients and decreased in others, indicating that nitroglycerin may have both beneficial and deleterious effects on distribution of flow. Some differences between the effects of intracoronary and intravenous nitroglycerin might have been expected because we compared different patient groups rather than administering nitroglycerin to each patient by the two routes. Nonetheless the effects of nitroglycerin on perfusion were remarkably similar regardless of the route administered.

Direct nitroglycerin effect on coronary circulation: The second important implication of these data is that nitroglycerin has a direct effect on the coronary circulation, as evidenced by the significant changes in the group receiving intracoronary nitroglycerin (Fig. 1B). It is also apparent that there was no consistent trend of increased distribution of flow to those segments with improved wall motion. Although redistribution of flow could have been a factor in improving wall motion in a few patients, it could not explain improvement in most. A limitation of the intracoronary microsphere technique is that changes in distribution of flow are measured but absolute changes in flow are not. Therefore, absolute flow to the anterior wall could increase and improve wall motion without redistribution of flow to that region. In view of the possibility of coronary vasodilatation by nitroglycerin, it would have been desirable to have a measure of absolute coronary flow in these studies. However, the reduction in blood pressure observed in all the patients with improved motion would lower coronary perfusion pressure and make increased coronary flow past significant arterial stenosis less likely. This is consistent with the findings of Bernstein et al.,[8] who demonstrated that intracoronary nitroglycerin in dogs resulted in an early increase in coronary flow that did not persist after arterial pressure decreased. Similarly, Gorlin et al.[12] found that nitroglycerin increases coronary flow in normal subjects but not in patients with coronary artery disease.

Effect of coronary collateral vessels: The other potential source of error in assessing distribution of flow could be the effect of collateral vessels. It is possible that left anterior descending arterial flow could be augmented by collateral flow from the right coronary system without being measured by this technique, since no particles were injected into the right coronary artery. However, only 4 of the 13 patients with reversible asynergy had collateral vessels to the left anterior descending artery, and in fact none of the intracoronary nitroglycerin group. Hence, collateral flow, although possibly playing a role in some, was not a factor in most patients in this study.

Implications: We found that both systemic and intracoronary nitroglycerin improved wall motion of hypokinetic ventricular segments in nearly half of the patients studied. Nitroglycerin resulted in both increases and decreases in distribution of flow to these areas, but these changes in flow did not correlate with changes in wall motion. The one consistent feature in patients with improved wall motion was a decrease in systemic pressure, suggesting that the systemic effect, especially afterload reduction, is the most important effect of nitroglycerin in producing improved wall motion.

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Hemodynamic Effects of Molsidomine at Rest and During Submaximal and Maximal Exercise in Patients With Coronary Artery Disease Limited by Exertional Angina Pectoris

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To analyze the mechanisms of action of molsidomine, a new antianginal drug, 10 patients with coronary artery disease and exertional angina pectoris were studied. Hemodynamic measurements were made at rest, during submaximal exercise and during angina-limited exercise before and 1 hour after intravenous administration of 2 mg of molsidomine. When angina pectoris was prevented after the drug was given (6 of 10 patients), the exercise intensity was increased until the recurrence of angina (3 patients) or until exhaustion (3 patients), and hemodynamic data were recorded at this higher exercise capacity.

At rest and during submaximal exercise, molsidomine increased heart rate and decreased cardiac output and mean systemic and pulmonary arterial pressures. The prevention of angina pectoris was attended by lower mean systemic and pulmonary arterial pressures and pressure-rate product; cardiac output and heart rate were unchanged. The greater exercise capacity (+26 percent) after molsidomine was attended by increases in maximal cardiac output (+19 percent) and in arteriovenous oxygen difference (+6 percent); the maximal pressure-rate product was unchanged and systemic vascular resistance was lower. The mechanisms of action of molsidomine are very similar to those of nitrates and imply a decrease in venous and arterial tone. Molsidomine deserves further study in patients with angina or congestive heart failure.

Molsidomine (N-ethoxycarbonyl-3-morpholine-sydnonimine) is a promising new antianginal drug that was introduced in West Germany in 1978. From the available data, the effects of molsidomine are similar to those of nitrates, but they last 5 to 8 hours after oral, sublingual or intravenous administration.[1–8] Previous hemodynamic studies in human beings have shown that at rest molsidomine decreases both the preload and the afterload of the left ventricle;[6–8] at rest the decrease in arterial blood pressure is accompanied by a similar decrease in cardiac output and, consequently, the calculated peripheral resistances appear unchanged.[9–11] These data are in agreement with data from animal studies indicating that the long-lasting hypotensive action of molsidomine is primarily due to a dilation of the capacitance vessels.[12–24]

During exercise, molsidomine induces a moderate decrease in the mean arterial pressure and a marked decrease in the mean pulmonary arterial pressure[6–8] but the effects on cardiac output have not been measured. The goal of this study was to explore the hemodynamic modifications underlying the increase in physical working capacity induced by molsidomine in patients with coronary artery disease limited by exertional angina pectoris.

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TABLE I

Clinical Data in 10 Patients

Case	Age (yr)	Prior MI	Coronary Arteriography*				Left Ventriculography			EF (%)
			LM	LAD	LCx	RCA	Ant Wall	Apical Wall	Inf Wall	
1	56	Inf	Not performed†				Not performed			...
2	54	Inf	—	50	—	95	—	—	A	50
3	44	—	—	75	O	O	H	—	—	78
4	55	—	50	75	O	O	—	—	A	68
5	55	Ant, inf	—	80	—	O	—	A	D	27
6	49	—	—	80	80	50	—	—	—	67
7	58	Ant	—	O	O	75	—	A	H	51
8	61	Inf	—	90	—	O	—	A	A	45
9	48	—	80	90	—	—	—	—	—	81
10	52	Ant	—	O	90	—	A	A	—	47

* % Stenosis or O = occluded. † Thallium-201 scintigraphy at rest and during exercise in this patient showed a permanent defect in the inferior region and transient hypoperfusion in the anteroseptal region.

A = akinesia; Ant = anterior; D = dyskinesia; EF = ejection fraction; H = hypokinesia; Inf = inferior; LAD = left anterior descending artery; LCx = left circumflex artery; LM = left main coronary artery; MI = myocardial infarction; RCA = right coronary artery.

Methods

Study patients: Ten men with documented coronary artery disease and exertional angina pectoris were studied (Table I); these patients were selected from a larger group of 20 consecutive patients with angina pectoris who were randomly allocated to this or a similar study on nifedipine. Patients with symptoms or clinical signs of congestive heart failure were excluded.

The aim of this study was carefully explained to the patients, and all gave consent. It was begun 1 week before or 1 week after the angiographic study; no complications occurred as a result of the experimental procedure.

Protocol: The patients first performed a multistage bicycle exercise test in the sitting position; the initial work load of 20 watts during 1 minute was increased by 20 watts every minute. Exercise was continued until the onset of typical angina pectoris; 1 minute samples of expiratory gases were collected during the last 3 to 4 minutes of the exercise (see later). Electrocardiographic leads V_4, V_5 and V_6 were monitored on an oscilloscope and recorded on paper every minute; a 12 lead electrocardiogram was recorded at rest, at peak exercise level and at the 2nd and 5th minutes of recovery. The electrocardiographic tracings were visually analyzed as previously described:[15] The amount of horizontal or downsloping S-T segment depression was measured in the most abnormal lead at the J point with the P-R level used as zero reference; the S-T segment abnormalities already present at rest were subtracted from the observed changes.

On the following day, hemodynamic measurements were taken (see later) with patients in the sitting position at rest and during two levels of exercise; each level lasted 4 to 6 minutes. The intensity of the first exercise level was well below the threshold of angina; the intensity of the highest exercise level was selected from the results of the first exercise test so that angina was induced after 3 to 4 minutes. Hemodynamic data were thus obtained at rest, during submaximal exercise and during exertion-induced angina. After completion of these measurements, the patients were given 2 mg of molsidomine intravenously and they rested in a supine position for 1 hour.

One hour after administration of molsidomine, the protocol was repeated. When angina was no longer precipitated at the work level that precipitated it before treatment with molsidomine, the hemodynamic measurements were performed at this level and the work load was then increased by 20 watts/min until angina pectoris or the first signs of exhaustion appeared; that level of exercise was maintained for 4 to 5 minutes until hemodynamic measurements were completed.

Hemodynamic measurements: Cardiac output was measured as previously described,[16] at rest and during the last minute of each exercise period using the Fick principle. Briefly, a 7 Swan-Ganz balloon-tip catheter was percutaneously introduced in the basilic vein and floated in the pulmonary artery; a small Teflon® catheter was introduced in the brachial artery. The pressures were measured during the 20 seconds preceding the cardiac output measurements with Statham P23Db transducers; the fourth intercostal space in the sitting position was the zero level. The expiratory gases were collected in neoprene bags; oxygen and carbon dioxide concentrations were determined as previously described[17] by a paramagnetic oxygen analyzer (Servomex OA 150) and by an infrared absorption carbon dioxide analyzer (Capnograph Godart 160). Expiratory volume was determined with a dry gas meter (Parkinson and Cowan, CD 4). The arterial and mixed venous oxygen contents were determined with a Lex-O_2CON analyzer.[18]

Precautions were taken to control the factors that might have influenced the response to exercise. The experiments took place in an air-conditioned room with temperature of 22° C (±1° C) and relative humidity of 50 percent (±10 percent). Before their first control exercise test, all patients had already performed at least one exercise test during the preceding weeks in the same room and with the same staff; the exercise studies reported here were all supervised by the same physician and the atmosphere of the laboratory was kept as quiet as possible.

The following hemodynamic variables were calculated: pressure-rate product: Heart rate × mean brachial pressure × 10^{-2}, expressed in mm Hg/min; *systemic and pulmonary resistances:* Mean pressure × 80/cardiac output, expressed in dynes/cm^{-5} per s; and *stroke work:* Stroke volume × mean brachial pressure × 1.36 × 10^{-2}, expressed in g-m.

Significances of differences were analyzed with the Student's paired *t* test.

TABLE II

Data Collected at the Maximal (Max) Exercise Level Before and After Molsidomine

Case	Work Load (watts/min)	$\dot{V}O_2$SL or Max (ml/min)	Heart Rate (beats/min)	Angina Pectoris	S-T Depression (mm)
1					
C	60	801	115	Yes	2.0
B	60	859	148	Yes	2.0
A	60	870	160	Yes	2.5
2					
C	160	1721	145	Yes	2.0
B	160	2112	148	Yes	1.0
A	160	2227	150	Yes	1.0
3					
C	100	1169	150	Yes	4.0
B	90	1192	144	Yes	3.5
A	90	1259	142	Yes	3.5
4					
C	100	1174	120	Yes	4.0
B	80	1331	135	Yes	4.0
A	80	1307	130	Yes	4.0
5					
C	140	1537	175	Yes	2.0
B	100	1430	165	Yes	2.0
A	120	1729	180	No	2.0
6					
C	100	1158	124	Yes	2.0
B	70	996	130	Yes	1.0
A	90	1262	142	Yes	1.0
7					
C	100	1159	135	Yes	0.5
B	80	1244	115	Yes	1.0
A	120	1541	152	No	0.5
8					
C	100	1153	130	Yes	3.0
B	40	722	115	Yes	7.0
A	80	1416	135	Yes	3.0
9					
C	200	2044	150	Yes	1.0
B	150	1864	145	Yes	2.0
A	250	3088	185	No	—
10					
C	120	1353	150	Yes	2.0
B	80	1052	158	Yes	2.0
A	110	1493	172	Yes	2.0
Mean					
C	118	1330	139	10/10	2.2
B	91	1280	140	10/10	2.4
A	116	1619	155	7/10	1.7
p					
C,B	<0.005*	NS	NS	. . .	NS
B,A	<0.05	<0.02	<0.02	. . .	NS

* The higher control work load is simply due to the use of a different type of exercise test: stepwise (20 watts/min) increase in the work load during the control test and rectangular work loads for 4 to 6 minutes during the hemodynamic study.

B and A = before and after administration of molsidomine (hemodynamic study); C = control exercise test; NS = not significant; p = probability; S-L = symptom-limited.

Results

Exercise capacity: The individual data on maximal exercise capacity are presented in Table II. The symptom-limited oxygen consumption ($\dot{V}O_2$) and the maximal heart rate measured before administration of molsidomine during the hemodynamic study did not differ significantly from values measured during the first exercise test.

After molsidomine, the symptom-limited $\dot{V}O_2$ increased from 1,280 to 1,619 ml/min (+ 26 percent; $p < 0.02$), whereas the maximal heart rate was 15 beats higher (from 140 to 155 beats/min; $p < 0.02$). Angina was completely prevented in three patients and recurred at a higher exercise level in three other patients. The electrocardiographic abnormalities at the maximal exercise level were slightly but insignificantly lessened after molsidomine. A higher maximal work load after molsidomine was observed in six patients (Cases 5 to 10) whose average increase in physical working capacity was 44 percent (from 1,218 to 1,755 ml/min); four patients (Cases 1 to 4) had no change in physical capacity after administration of the drug. These four did not differ from the others with respect to age, history of myocardial infarction, number of diseased coronary vessels and ventricular function (Tables I and II).

Changes in hemodynamics at rest: The hemodynamic data are presented in Table III and Figure 1. At rest, in the sitting posture, the cardiac output averaged 4.9 liters/min and the mean cardiac index was 2.6 li

TABLE III

Hemodynamic Data Before (B) and After (A) Molsidomine

	$\dot{V}O_2$	HR	CO	SV	avO_2	BaP	PaP	SR	PR	SW	Pressure-Rate Product	S-T↓
Rest Sitting (n = 10)												
B	315 ± 56	79 ± 15.8	4.9 ±0.86	65 ± 24.4	6.5 ± 1.02	109 ± 12.1	18 ± 2.6	1823 ± 369	303 ± 64	95 ± 33.4	87 ± 24	−0.3 ± 0.58
A	322 ± 78	98 ± 19.8	3.7 ± 0.59	39 ± 6.3	8.7 ± 1.43	85 ± 11.1	16 ± 2.0	1843 ± 280	347 ± 57	44 ± 7.8	84 ± 23	−0.3 ± 0.35
Δ	+7	+19	−1.2	−26	+2.2	−24	−2	+20	+44	−51	−3	−
p	NS	<0.001	<0.01	<0.005	<0.001	<0.001	<0.001	NS	NS	<0.005	NS	NS
Submaximal Exercise (n = 9)												
B	791 ± 201	100 ± 17.6	8.0 ± 0.99	82 ± 18.8	10.1 ± 1.45	119 ± 14.1	26 ± 6.1	1249 ± 341	276 ± 94	130 ± 25.0	120 ± 34	−0.6 ± 0.82
A	785 ± 185	109 ± 16.0	7.0 ± 2.54	65 ± 11.6	11.2 ± 1.59	97 ± 13.5	20 ± 30	1124 ± 198	230 ± 39	85 ± 16.9	106 ± 25	−0.5 ± 0.87
Δ	−6	+9	−1.0	−27	+1.1	−23	−6	−125	−46	−45	−14	−0.1
p	NS	<0.02	<0.05	<0.02	<0.05	<0.001	<0.02	NS	NS	<0.001	<0.01	NS
Maximal Exercise (n = 10)												
B*	1280 ± 433	140 ± 16.6	9.4 ± 2.10	67 ± 15.3	13.5 ± 2.40	131 ± 20.7	38 ± 12.5	1153 ± 222	350 ± 169	121 ± 36.0	184 ± 38	−2.4 ± 2.02
A												
Same WL (2)	1324 ± 514	140 ± 12.7	9.6 ± 2.29	69 ± 18.1	13.6 ± 2.56	116 ± 20.3	30 ± 7.7	984 ± 184	261 ± 105	109 ± 33.8	162 ± 42	−1.3 ± 1.63
Δ (1)–(2)	+44	...	+0.2	+2	+0.1	−15	−8	−169	−89	−12	−21	−1.1
p (1)–(2)	NS	NS	NS	NS	NS	<0.001	<0.05	<0.02	NS*	NS*	<0.02	NS
Higher WL(3)	1619 ± 625	155 ± 19.0	11.2 ± 3.39	73 ± 17.7	14.3 ± 2.60	123 ± 14.7	34 ± 11.5	925 ± 204	267 ± 129	122 ± 35.3	191 ± 35	−1.7 ± 1.46
Δ (1)–(3)	+339	+15	+1.8	+7	+0.8	−8	−4	−228	−83	+1	+7	−0.7
p (1)–(3)	<0.02	<0.02	NS*	NS	<0.02	NS*	NS	<0.01	<0.005	NS	NS	NS

* $0.05 < p < 0.10$.

avO2 = arterial mixed venous oxygen difference (ml/100 ml); BaP = mean brachial arterial pressure (mm Hg); CO = cardiac output (liters/min); Δ = difference; HR = heart rate (beats/min); NS = not significant; p = probability; PaP = mean pulmonary arterial pressure (mm Hg); pressure-rate product = heart rate × mean brachial arterial pressure (mm Hg/min^{-2}); PVR = pulmonary vascular resistance (dynes sec cm^{-5}); ST↓ = S-T segment depression (mm); SV = stroke volume (ml/beat); SVR = systemic vascular resistance (dynes sec cm^{-5}); SW = stroke work (g·m) = stroke volume × mean brachial arterial pressure; $\dot{V}O_2$ = myocardial oxygen consumption (ml/min); WL = work load.

ters/min per m^2 (range 2.2 to 3.4). The mean pulmonary arterial pressure was 18 mm Hg and the pulmonary end-diastolic pressure 11 mm Hg (range 8 to 16 mm Hg).

After molsidomine (Table III, Fig. 1) cardiac output and stroke volume decreased whereas the heart rate increased; because the oxygen consumption was unchanged, the arteriovenous oxygen differences increased. The mean arterial and pulmonary pressures were lower but, because of the decreased cardiac output, the vascular resistances were unmodified. The stroke volume and the pressure-rate product were reduced after molsidomine.

Changes in hemodynamics at submaximal exercise: The changes observed after molsidomine during submaximal exercise were similar but less pronounced than those noted at rest (Table III, Fig. 1). Because the increase in heart rate was less (+9 beats/min) and the decrease in blood pressure was the same as at rest, the pressure-rate product was significantly decreased at submaximal exercise.

Changes in hemodynamics at maximal exercise: The work load causing angina pectoris in all patients in the control study was often (6 of 10 patients) performed after molsidomine without anginal pain. The prevention of angina pectoris was accompanied by significant decreases in pulmonary and mean arterial pressure, stroke work, pressure-rate product and systemic vascular resistance (Table III). The electrocardiographic signs of myocardial ischemia also tended to be reduced (difference not significant [NS]). The cardiac output and the heart were unmodified at that exercise level.

At the maximal exercise level, the increased oxygen consumption (+ 26 percent) was due to a greater cardiac output (+19 percent; p = NS; p <0.10) and to a wider arteriovenous oxygen difference (+6 percent). The mean arterial pressure remained slightly reduced after molsidomine and, accordingly, the peripheral vascular resistance was decreased; the mean pulmonary arterial pressure was slightly decreased (p = NS) and the pressure-rate product was insignificantly increased.

All the changes in mean pulmonary arterial pressure noted in this study closely reflected changes in the mean capillary wedge pressure or in the pulmonary end-diastolic pressure, or both. These variables decreased from 11.5 to 9.5 mm Hg at rest (p = 0.01; n = 9), from 18.5 to 13.5 mm Hg at submaximal exercise (p = 0.05; n = 6) and from 23 to 10 mm Hg at maximal exercise (p = NS; n = 4).

Discussion

Our data indicate that the effects of molsidomine in patients with coronary artery disease and angina pectoris are similar to those induced at rest and during

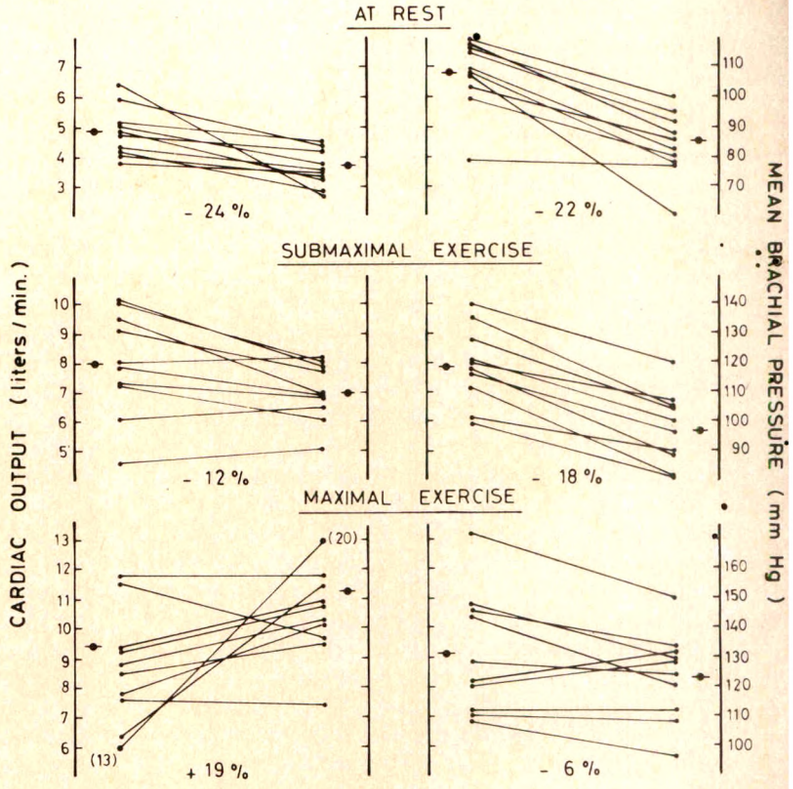

FIGURE 1. Cardiac output (**left panel**) and mean brachial pressure (**right panel**) in 10 patients at rest and during exercise before and after administration of 2 mg of molsidomine.

exercise by nitroglycerin or nitrates. These hemodynamic and clinical data were observed 1 hour after intravenous administration of 2 mg of molsidomine.

Reliability of the testing protocol: Our patients had severe coronary artery disease, indicated in all by angina pectoris and abnormal electrocardiographic responses to exercise. The diagnosis was ascertained in 9 of the 10 patients with angiographic data and in one patient with an abnormal thallium-201 scintigram demonstrating a permanent defect and a transient area of hypoperfusion. Their angina pectoris was stable and was induced at a highly reproducible heart rate and total level of oxygen consumption during two control exercise tests performed on consecutive days, the first without and the second with intravascular catheters. These patients had no signs of heart failure and their baseline hemodynamic data collected at rest and in a sitting posture are similar to those previously reported in patients with coronary artery disease and angina pectoris.[19]

The protocol of the hemodynamic studies included a first period of light exercise followed by a higher work load that induced angina pectoris in all patients in 3 to 5 minutes; this protocol is similar to that recommended by Redwood et al.[20] for studying the efficacy of a therapeutic intervention in patients with angina. With respect to cardiac output and measurements of stroke volume and central pressure during exercise, their reproducibility is good when the time elapsed between two exercise tests is long enough[17,21]; this time interval should not be less than 30 minutes and ideally should be 60 minutes in order to eliminate the hemodynamic modifications observed during repeated exercise.[17,22] Thus, the hemodynamic modifications observed in our study can safely be attributed to the effect of the drug and not to a placebo effect or the simple repetition of the exercise test.

Hemodynamic changes during exercise-induced angina: During exertional angina pectoris, most patients with coronary artery disease have clear signs of depressed left ventricular function as indicated by a marked elevation of the left ventricular end-diastolic pressure, pulmonary capillary wedge pressure or mean pulmonary arterial pressure.[26–29] These abnormalities, accompanied by a leveling or a decrease in stroke volume and stroke work, are similar to those observed during maximal exercise in patients with coronary artery disease not limited by angina pectoris;[16,30] however, in patients limited by angina, abnormalities occur at a decreased external work load and heart rate.[29] These hemodynamic abnormalities are caused by transient myocardial ischemia that depresses left ventricular function and probably also modifies left ventricular geometry, compliance and relaxation.[31–34] At a submaximal level of exercise, performed without pain, the hemodynamic response is intermediate and the importance of the hemodynamic disorders appears to be determined by the degree of left ventricular impairment at rest.[29,35,36]

Hemodynamic effects of molsidomine during rest and exercise: At rest and in a sitting posture, molsidomine decreased cardiac output and mean arterial and

pulmonary pressure in all our patients; these effects noted in patients with coronary artery disease without congestive heart failure confirm previous hemodynamic observations on molsidomine.[6–11] Thus, at rest, molsidomine seems to have a predominant action on venous return leading to a significant decrease in cardiac output accompanied by a reflex increase in heart rate. Systemic vascular resistances were not modified because at rest the decrease in cardiac output (−24 percent) was of the same magnitude as the decrease in mean arterial pressure (−22 percent). These changes are similar to those induced at rest by nitrates in patients without congestive heart failure.[21,27,28,37,38]

At submaximal exercise, the hemodynamic modifications noted after molsidomine were similar but clearly less marked than those at rest; the small decrease (−12 percent) in cardiac output indicated a persistent decrease in venous return, probably due to the dilating action of the drug on the venous wall. The intensity of the submaximal exercise level used in our study probably influenced the data because there was a progressive change in the hemodynamic effects of the drug from rest to maximal exercise, namely, a trend from a decrease in cardiac output at rest to an increase in cardiac output at the maximal exercise level. Had we used a submaximal exercise level of greater intensity, one can reasonably presume that the cardiac output would have been unchanged, as observed after administration of nitrates.[28,37,38]

Effects of molsidomine on angina pectoris and ventricular function: Our study includes hemodynamic data at the symptom-limited exercise level before and at that same level of exercise after administration of molsidomine. The prevention of angina pectoris in 60 percent of the patients after molsidomine was attended by a marked decrease in the mean pulmonary arterial pressure with no change in cardiac output; the mean arterial pressure was lower as were the systemic vascular resistances. The observed improvement in left ventricular function likely reflects a transient restoration or improvement of the equilibrium between the myocardial oxygen supply and requirements. Myocardial oxygen requirements are decreased (1) through a decrease in the mean arterial pressure and in the pressure-rate product, and (2) by a decreased left ventricular volume resulting from the reduced venous tone.[11] As a result, the hemodynamic and electrocardiographic alterations observed during angina pectoris were largely prevented and the majority of patients were able to exercise at higher external work loads before reonset of angina pectoris or until exhaustion without recurrence of anginal pain. Similar data have been collected after administration of nitrates.[21,25–28,40–45]

Mechanisms of action of molsidomine: After molsidomine, the physical capacity of our patients (as measured by symptom-limited oxygen consumption [$\dot{V}O_2$]) increased by 26 percent, which is similar to the antianginal effects noted by other investigators after administration of oral or sublingual molsidomine[2,3,5] and oral or sublingual nitrates.[2,3,5,23–25] This 26 percent increase in physical capacity is explained by a wider arteriovenous oxygen difference (+6 percent) and by a greater maximal cardiac output (+19 percent), which is associated with a higher maximal heart rate (+11 percent). At this postdrug maximal exercise level, the mean arterial pressure remained reduced (−6 percent) and the pressure-rate product tended to be increased (+4 percent). Other studies found that the antianginal action of molsidomine[3,4] or nitrates[23–25,39] was attended by a moderate increase in the maximal pressure-rate product. At this higher maximal exercise level, the effects of molsidomine on the venous tone are masked because, by definition, the increased maximal cardiac output postulates a greater venous return. The major mechanism of action of molsidomine at maximal exercise therefore appears to be a decrease in afterload, as suggested by lower systemic resistance. Both mechanisms (namely, decreased venous and arterial tone) are probably effective, but they mask each other in one direction at rest and in the opposite direction at maximal exercise. In any event, myocardial ischemia is delayed or prevented after drug administration.

Implications: After administration of molsidomine, 40 percent of our patients showed no improvement; the same observation has repeatedly been made with nitrates. The size of our group is insufficient to elucidate the reasons for the ineffectiveness of the drug in some patients, and these are now under study in a larger group of patients. We conclude that the acute hemodynamic effects of molsidomine are similar to those of nitrates and they imply a decrease in the venous tone as well as a lower peripheral arterial resistance. This drug deserves further study in both patients with angina and those with congestive heart failure.

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Hemodynamics at Rest and During Exercise After Oral Hydralazine in Patients With Cor Pulmonale

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Oral hydralazine has been shown to be effective in decreasing pulmonary arteriolar resistance and increasing cardiac output in some patients with primary pulmonary hypertension. To determine whether a similar response could be observed in patients with chronic cor pulmonale, the hemodynamic status before and after the oral administration of hydralazine (25 mg, then 50 mg every 6 hours for 48 hours) were evaluated in 12 patients at rest and in 8 during upright exercise. After hydralazine, there was an increase in cardiac output at rest, from 4.3 to 6.3 liters/min ($p < 0.001$), and reductions in arteriovenous oxygen difference, from 8.1 to 6.1 volume percent ($p < 0.001$), mean pulmonary arterial pressure, from 52 to 44 mm Hg ($p < 0.01$), and pulmonary arteriolar resistance, from 11.2 to 6.2 units ($p < 0.0005$). Similar hemodynamic changes occurred during exercise, including an increase in pulmonary arterial saturation from 27 to 39 percent ($p < 0.001$) and a decrease in total pulmonary resistance from 12.7 to 8.9 units ($p < 0.01$). Results of pulmonary function tests performed before and after hydralazine did not change with drug administration. These findings indicate that the lung vascular bed in some patients with cor pulmonale is capable of responding to hydralazine with a reduction in pulmonary resistance and an increase in cardiac output both at rest and during exercise.

Pulmonary hypertension can complicate various forms of chronic lung disease and, next to coronary artery disease and hypertensive cardiovascular disease, cor pulmonale is the most common cardiac disorder beyond the 5th decade of life.[1] The treatment of cor pulmonale has primarily been aimed at optimizing intrapulmonary gas exchange with bronchodilators, corticosteroids, antibiotic agents and chest physiotherapy. Supplemental oxygen therapy causes a reduction in pulmonary arterial pressure in some patients with hypoxemia and cor pulmonale,[2–4] but the responsiveness of the pulmonary vascular bed to increased concentrations of inspired oxygen tends to diminish with prolonged use.[5] Diuretic drugs, often used to reduce preload and edema,[6] can cause metabolic derangements that are poorly tolerated by patients with pulmonary disease.[7,8] Although cardiac glycosides have been recommended for right ventricular failure,[9] the limited clinical response and the increased risk of toxicity associated with their use in the setting of chronic pulmonary disease make their role controversial.[10]

Vasodilators have been used for many years to treat systemic hypertension, and in the last few years have gained acceptance for treatment of left ventricular failure. Attention has recently been paid to the usefulness of some vasodilators in treating idiopathic pulmonary hypertension.[11] However, there is little experience with these drugs in treating pulmonary hypertension secondary to chronic lung disease. This study evaluates the effects of oral hydralazine on the hemodynamic status at rest and during exercise in patients with cor pulmonale, to determine the potential usefulness of this drug as an adjunct to the conventional therapy of pulmonary heart disease.

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Methods

Study patients: Twelve patients with stable chronic lung diseases and pulmonary hypertension were evaluated between November 1977 and April 1980. On the basis of the clinical data (Table I), the patients were classified as having one of three types of ventilatory defect: obstruction, restriction or mixed obstruction and restriction. Four of the five patients with obstructive airways disease had chronic bronchitis and one patient had asthma. Both patients with a restrictive ventilatory defect had interstitial pulmonary fibrosis, which was documented by lung biopsy. One of the patients with a mixed ventilatory defect had scleroderma in addition to chronic bronchitis, one had chronic bronchitis and a history of tuberculosis for which he had undergone a thoracoplasty 30 years previously, two patients had a mixed defect from undetermined causes, and one patient had sarcoidosis. None of the 12 patients had a history of myocardial infarction or known coronary artery disease. All of the patients underwent routine pulmonary function studies during a stable period in their course. The testing procedures used and the predicted normal values derived for each patient followed the accepted guidelines for pulmonary function testing.[12]

All of the patients were treated with conventional therapy for at least 6 months before the study. This therapy was continued unaltered during the period of hospitalization. Supplemental oxygen therapy was discontinued just before and throughout each cardiac catheterization procedure. Treatment consisted of administration of bronchodilators, antibiotic agents, supplemental oxygen, corticosteroids, diuretic drugs and digitalis compounds, as each patient's clinical status indicated. No patient had an acute respiratory or cardiac condition at the time of study or a history of previous myocardial infarction. None had valvular heart disease or clinical left ventricular failure. Informed consent, in compliance with the Medical Center Committee for Clinical Investigations, was obtained from each patient before the study.

Hemodynamic measurements: Right heart catheterization was performed using a balloon-tipped flotation catheter inserted into an antecubital or internal jugular vein. A plastic catheter was inserted into a brachial or radial artery for recording systemic pressure and sampling arterial blood. Measurements of supine right atrial, right ventricular, pulmonary arterial and pulmonary capillary wedge pressures were made by averaging the values over at least three respiratory cycles. Mean pressures were calculated by adding one third of the pulse pressure to the diastolic pressure. Timed collections of exhaled volume during tidal breathing were measured in a gasometer and the volumes converted to STPD (standard temperature and pressure, dry). The oxygen content of the exhaled gas was measured using a paramagnetic oxygen analyzer (Beckman Instruments), and from these data, we calculated total body oxygen consumption. Simultaneous arterial and mixed venous blood samples were collected anaerobically in heparinized syringes and their oxygen contents were determined using an IL-282 Co-oximeter (Instrument Labora-

TABLE I

Pulmonary Function Data From 12 Patients With Cor Pulmonale

Case	Age (yr) & Sex	FVC (liters)	FEV_1 (liters)	MMFR (liters/min)	TLC (liters)	RV (liters)	D_LCO (ml/min per mm Hg)	Arterial Blood Gases* pH (units)	pCO_2 (torr)	pO_2 (torr)
					Chronic Obstructive Lung Disease					
1	59M	3.35 (77%)	1.84 (56%)	0.85 (27%)	5.23 (82%)	1.88 (81%)	—	7.36	37	45
2	57M	1.29 (36%)	0.48 (18%)	0.22 (7%)	8.17 (158%)	7.06 (441%)	—	7.47	43	49
3	65M	1.31 (34%)	0.62 (21%)	0.33 (11%)	4.09 (73%)	2.82 (162%)	—	7.40	48	55
4	63M	2.17 (47%)	0.85 (27%)	0.53 (7%)	8.01 (123%)	5.84 (300%)	—	7.40	37	47
5	62M	1.91 (45%)	0.52 (16%)	0.16 (8%)	8.66 (136%)	6.75 (291%)	—	7.45	34	63
					Chronic Restrictive Lung Disease					
6	64M	1.91 (45%)	1.02 (35%)	0.34 (12%)	4.84 (74%)	3.38 (145%)	7.0 (27%)	7.44	42	58
7	55M	2.50 (59%)	2.11 (84%)	2.79 (87%)	4.09 (68%)	1.59 (76%)	6.0 (15%)	7.51	34	57
					Mixed Obstruction and Restriction					
8	48F	2.54 (94%)	1.47 (65%)	0.99 (29%)	4.18 (118%)	1.67 (197%)	3.3 (17%)	7.43	26	71
9	57M	1.58 (37%)	1.37 (42%)	2.39 (79%)	4.78 (166%)	3.14 (42%)	12.6 (42%)	7.37	40	54
10	65M	1.40 (40%)	0.92 (36%)	0.61 (20%)	2.67 (53%)	1.43 (92%)	—	7.44	43	61
11	64M	3.78 (84%)	2.60 (83%)	1.39 (47%)	5.85 (84%)	2.08 (84%)	17.3 (65%)	7.51	27	62
12	44M	2.03 (43%)	1.28 (36%)	0.73 (20%)	3.21 (48%)	1.26 (63%)	14.9 (52%)	7.47	34	75

* Determined while the patients were breathing room air.

D_LCO = single breath study of carbon monoxide transfer; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; MMFR = maximal mid expiratory flow rate; PCO_2 and PO_2 = partial pressure of carbon dioxide and oxygen, respectively; RV = residual volume; TLC = total lung capacity. Percentage values represent the percent of predicted normal for each value, based on age, sex and height.

TABLE II

Hemodynamic Data Obtained at Rest (12 patients)

Case	Pressures (mm Hg) BA	PA	RA	RVEDP	PCW	BA Sat (%)	PA Sat (%)	avO_2 (vol%)	$\dot{V}O_2$ (ml/min)	CO (liters/min)	HR (beats/min)	PAR (units)	TPR (units)	TSR (units)
1†														
C	155/84 (106)	43/24 (31)	3	4	8	87	54	6.5	341	5.2	120	4.4	6.0	20.3
H	113/72 (86)	35/18 (24)	3	3	10	85	57	5.4	382	7.0	114	2.0	3.4	12.3
2*														
C	116/75 (89)	39/22 (28)	4	6	8	75	47	5.2	346	6.7	120	3.0	4.2	13.3
H	125/65 (85)	38/24 (28)	4	5	7	78	58	3.5	285	8.2	120	2.5	3.4	10.4
3†														
C	124/86 (98)	88/46 (60)	9	8	15	72	39	8.4	275	3.3	110	13.6	18.2	29.7
H	110/80 (90)	78/43 (55)	4	6	16	78	55	6.2	490	7.9	120	4.9	7.0	11.4
4†														
C	135/71 (92)	65/36 (46)	7	8	7	85	52	7.5	354	4.7	100	8.3	9.8	19.6
H	167/82 (110)	57/36 (43)	5	5	7	86	63	5.7	399	7.0	108	5.1	6.1	15.7
5†														
C	117/83 (94)	47/34 (38)	6	8	16	96	46	8.6	473	5.5	108	4.0	6.9	17.1
H	92/57 (69)	37/17 (24)	4	5	13	99	55	6.8	444	6.5	120	1.7	3.7	10.6
6†														
C	232/150 (177)	80/51 (61)	8	12	16	89	50	10.2	464	4.6	102	9.8	13.3	38.5
H	184/120 (141)	65/33 (44)	7	10	13	91	59	5.9	501	8.5	96	3.6	5.2	16.6
7†														
C	150/89 (109)	97/41 (60)	15	22	10	86	47	7.9	425	5.4	96	9.3	11.1	20.2
H	126/81 (96)	73/45 (54)	12	20	11	88	58	6.9	407	5.9	90	7.3	9.1	16.3
8†														
C	138/82 (101)	105/52 (70)	8	16	10	93	36	10.1	253	2.5	102	24.0	28.0	40.4
H	133/76 (95)	98/45 (63)	9	13	10	93	54	7.7	280	3.6	108	14.7	17.5	26.4
9*														
C	108/72 (84)	116/61 (79)	11	12	10	76	34	8.4	288	3.4	96	20.3	23.2	24.7
H	113/70 (84)	86/54 (64)	11	9	10	84	51	6.2	274	4.4	96	12.3	14.5	19.1
10*														
C	130/72 (91)	84/34 (51)	3	2	12	88	69	3.8	213	5.6	80	7.0	9.1	16.2
H	130/60 (83)	45/20 (29)	3	2	10	88	73	3.1	232	7.5	104	2.5	3.9	11.1

TABLE II (Continued)

Case	Pressures (mm Hg) BA	PA	RA	RVEDP	PCW	BA Sat (%)	PA Sat (%)	avO_2 (vol %)	$\dot{V}O_2$ (ml/min)	CO (liters/min)	HR (beats/min)	PAR (units)	TPR (units)	TSR (units)
11*														
C	127/76 (93)	77/43 (54)	19	25	8	92	34	11.1	255	2.3	120	20.0	23.5	40.4
H	96/51 (66)	97/30 (51)	12	10	8	91	44	8.7	327	3.8	87	11.3	13.4	17.4
12†														
C	132/84 (100)	65/40 (48)	4	4	11	96	56	9.3	342	3.6	90	10.3	13.3	27.7
H	140/84 (102)	76/45 (55)	2	3	10	96	67	6.8	458	6.7	108	6.7	8.2	15.2
Mean‡														
C	103 ± 24	52 ± 15	8 ± 5	10 ± 7	11 ± 3	86 ± 8	47 ± 10	8 ± 2	336 ± 84	4.3 ± 1	103 ± 12	11.2 ± 7	13.9 ± 7	25.6 ± 9
H	92 ± 20	44 ± 15	6 ± 4	7 ± 5	10 ± 3	88 ± 6	58 ± 7	6 ± 1	373 ± 92	6.3 ± 2	106 ± 12	6.2 ± 4	7.9 ± 5	15.2 ± 5
p	<0.05	<0.01	<0.05	<0.05	NS	NS	<0.0001	<0.001	NS	<0.001	NS	<0.0005	<0.0005	<0.001

* Supine. † Sitting. ‡ ± Standard deviation.
avO_2 = arteriovenous oxygen difference; BA = brachial arterial pressure; BA Sat = brachial arterial saturation; C = control, CO = cardiac output; H = hydralazine; HR = heart rate; NS = not significant; p = probability; PA = pulmonary arterial pressure (systolic and diastolic with mean in parentheses); PAR = pulmonary arteriolar resistance; PA Sat = pulmonary arterial saturation; PCW = pulmonary capillary wedge pressure; RA = mean right atrial pressure; RVEDP = right ventricular end-diastolic pressure (in the supine position); TPR = total pulmonary resistance; TSR = total systemic resistance; $\dot{V}O_2$ = total body oxygen consumption.

tories). Cardiac output was calculated using the Fick equation.

Exercise testing: Eight of the patients were also studied at rest in the sitting position and during a period of exercise. After measurements in the supine position were made, each of these patients was placed in the sitting position on a bicycle ergometer. The pressure transducer level was adjusted to the reference point of zero pressure and the transducer height was recorded so that an identical level would be used for each patient's repeat study. Systemic and pulmonary arterial and pulmonary capillary wedge pressures and cardiac output were measured during seated rest. The patient then pedaled the bicycle for 3 minutes at 150 kilopond-meters/hour, and pulmonary and systemic arterial pressures and cardiac output were measured during the final minute of exercise. Previous experience in our laboratory has demonstrated that this degree of exercise causes at least a doubling of the oxygen consumption at rest.[13,14]

Hydralazine therapy: After the initial cardiac catheterization, the patients were immediately given 25 mg of hydralazine orally. When this dose was tolerated without significant adverse effects, they were then given hydralazine, 50 mg orally every 6 hours. Hemodynamic studies were repeated 48 hours after beginning therapy with hydralazine. The last dose of hydralazine before restudy was always given 1 to 2 hours before cardiac catheterization. Systemic and pulmonary vascular resistance were calculated using the standard formulas. Heart rate was obtained from a continuously monitored electrocardiogram. Statistical analysis of the data was performed with use of Student's two-tailed t test for paired data.

Results

Hemodynamic data at rest (Table II): All 12 patients had elevated pulmonary arterial pressure and pulmonary arteriolar resistance. The patients with either a pure restrictive ventilatory defect or a mixed ventilatory defect had higher pulmonary arterial pressure than most patients with obstructive airways disease alone. The control arteriovenous oxygen difference was abnormal in 11 of the 12 patients, reflecting an inadequate cardiac output for the tissues' oxygen demands. Eight patients had elevated right ventricular end-diastolic pressures and three of these had clinical findings of right ventricular failure. Pulmonary capillary wedge pressure at rest was normal in all patients.

After the administration of hydralazine, there were statistically significant decreases in the mean pulmonary arterial pressure ($p < 0.01$), arteriovenous oxygen difference ($p < 0.001$) and pulmonary arteriolar and total pulmonary resistances ($p < 0.0005$). Cardiac output was increased and heart rate was not significantly changed. Mean stroke volume increased 40 percent. Systemic arterial pressure did decrease significantly, but without any adverse effects.

Hemodynamic data during exercise (Table III): Mean pulmonary arterial pressure increased in the eight patients studied during exercise, and this increase was significantly blunted by hydralazine. Although cardiac output increased with exercise relative to control values at rest, the arteriovenous oxygen difference was markedly increased for this degree of mild exercise. After hydralazine, cardiac output was significantly increased during exercise ($p < 0.05$), and stroke volume increased

by 30 percent. Mean systemic blood pressure and heart rate were not appreciably changed. The arteriovenous oxygen difference narrowed, and the total pulmonary resistance was decreased. Whereas pulmonary capillary wedge pressure could be obtained from only five patients during exercise (Cases 1, 3, 6, 7 and 12), the values remained within the normal range (mean 14 mm Hg).

Discussion

Hemodynamic improvement after hydralazine in cor pulmonale: Hydralazine is used to treat left ventricular failure because it decreases left ventricular afterload. Systemic resistance decreases and cardiac output increases and there is usually little change in systemic blood pressure in this setting.[15,16] However, in patients with systemic hypertension both systolic and diastolic blood presssure decrease. Our experience with hydralazine for primary pulmonary hypertension[14] suggested that patients with other disorders characterized by an increased afterload to the right ventricle, such as cor pulmonale, might obtain beneficial results with this drug in a manner analagous to that of patients with systemic hypertension or left ventricular failure. Our 12 patients with parenchymal lung disease and pulmonary hypertension showed an increased oxygen delivery to the tissues at a lower right ventricular afterload both at rest and during exercise after being treated with oral hydralazine. None manifested adverse effects that limited the drug's use. These observations are consistent with the hypothesis that hydralazine caused vasodilatation of the pulmonary resistance vessels, thereby reducing impedance to right ventricular

TABLE III

Hemodynamic Data Obtained During Exercise (8 patients)

Case	BA (mm Hg)	PA (mm Hg)	BA Sat (%)	PA Sat (%)	avO_2 (vol%)	$\dot{V}O_2$ (ml/min)	CO (liters/min)	HR (beats/min)	TPR (units)	TSR (units)
1										
C	122/73 (88)	56/29 (38)	81	29	10.5	938	8.8	140	4.3	10.0
H	100/62 (75)	46/30 (35)	78	28	9.9	913	9.1	120	3.8	8.2
3										
C	159/106 (124)	102/50 (67)	73	22	12.2	797	6.5	120	10.3	19.1
H	132/92 (105)	95/47 (63)	78	39	9.4	696	7.4	130	8.5	14.2
4										
C	153/86 (108)	84/48 (60)	76	35	8.6	653	7.6	120	7.9	14.2
H	182/92 (122)	79/38 (52)	79	41	7.7	563	7.3	110	7.1	16.7
5										
C	138/88 (105)	69/52 (58)	89	35	10.7	768	7.2	130	8.1	14.6
H	120/74 (89)	55/23 (34)	91	46	8.9	770	8.7	128	3.9	10.2
6										
C	184/120 (141)	104/55 (71)	82	28	15.3	725	4.7	120	15.1	30.0
H	172/94 (120)	91/48 (62)	79	39	9.3	927	10.0	114	6.2	12.0
7										
C	148/92 (111)	107/47 (67)	82	28	11.7	660	5.6	120	12.0	19.8
H	120/81 (94)	98/46 (63)	86	40	9.9	680	6.9	108	9.1	13.6
8										
C	142/70 (94)	123/68 (86)	91	20	13.2	468	3.6	132	23.9	26.1
H	148/86 (107)	123/59 (80)	88	31	11.0	418	3.8	150	21.0	28.1
12										
C	166/92 (116)	152/70 (98)	93	32	14.9	730	4.9	126	20.0	23.7
H	152/82 (105)	122/70 (87)	93	48	10.0	718	7.2	120	12.1	14.5
Mean*										
C	111 ±17	68 ±18	83 ±7	27 ±6	12.1 ±2.3	717 ±135	6.1 ±1.7	126 ±7	12.7 ±6.6	19.7 ±6.7
H	102 ±16	59 ±19	84 ±6	39 ±7	9.5 ±1.0	711 ±169	7.6 ±1.8	123 ±13	8.9 ±5.6	14.7 ±6.0
p	NS	<0.01	NS	<0.001	<0.05	NS	<0.01	NS	<0.01	NS

* ± standard deviation.
Abbreviations as in Table II.

flow and leading to an increased right ventricular output and peripheral oxygen delivery.

Patients who have left ventricular failure,[13,15–17] aortic insufficiency[18] or mitral insufficiency[19] with or without left ventricular dysfunction often manifest a reduction in the left ventricular filling pressure with hydralazine. Vasodilator therapy with hydralazine, for unclear reasons, may also cause a reduction in left ventricular end-diastolic pressure in some patients with mitral insufficiency.[19] It is possible that the small but statistically significant decreases in both mean right atrial and right ventricular end-diastolic pressures that we observed in our patients are a result of a decrease in tricuspid or pulmonary valve regurgitation secondary to pulmonary vasodilatation with hydralazine.

Several studies have demonstrated that the degree of pulmonary hypertension remains stable for prolonged periods of time in patients with cor pulmonale and stable respiratory function.[5,20,21] We therefore think it is likely that the hemodynamic improvement after 48 hours of hydralazine therapy was the result of this therapy in our patients with stable lung disease maintained on their previous regimen. The reduction in systemic arterial pressure and resistance after beginning hydralazine is consistent with the known systemic effects of this drug, but in the absence of left ventricular dysfunction, it was not the cause of the hemodynamic improvement we observed.

Role of vasodilation in pulmonary vascular disease and vasoconstriction: Some investigators have stressed the significance of the diminished pulmonary vascular bed in the development of pulmonary hypertension in obstructive[22] as well as restrictive[23] lung disease. Our demonstration that some patients with diverse causes for pulmonary hypertension, even those with interstitial pulmonary fibrosis, respond to vasodilator therapy suggests that there may be reversible constriction in addition to the restriction of the pulmonary vascular bed in this setting. If the cardiac output had increased and the pulmonary resistance decreased as a result of increased intrapulmonary shunting after hydralazine, arterial oxygenation would have decreased significantly; arterial oxygenation was not appreciably changed in our patients.

One major concern about vasodilator therapy for chronic cor pulmonale is the possibility of causing vasodilatation in areas of poor alveolar ventilation. This effect could worsen the hypoxemia of chronic lung disease by exaggerating the ventilation/perfusion imbalance already present. This phenomenon has been implicated in the increased alveolar/arterial oxygen gradient observed in patients receiving nitroglycerin[24] or nitroprusside.[25] However, the arterial oxygen contents were not appreciably changed by hydralazine in our patients, thus suggesting that the increased pulmonary blood flow, coupled with the greatly improved mixed venous saturation, offset any potential aggravation of ventilation perfusion mismatching. The contribution of a low mixed venous saturation to the development of hypoxemia in obliterative pulmonary vascular disease was recently emphasized by Dantzker and Bower.[26]

Hydralazine is a vascular smooth muscle relaxing agent, and we reasoned that it might also be a bronchial smooth muscle dilator as well. However, pulmonary function studies performed before and after hydralazine therapy failed to show any change in air flow rates.

Implications: The survival of patients with chronic pulmonary disease has been linked by several studies to the presence and degree of pulmonary hypertension.[20,27–29] Whether the use of effective vasodilators will alter the course of cor pulmonale is not known, but these agents may prove useful in its management.

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Clinical Pharmacology and Antiarrhythmic Efficacy of N-Acetylprocainamide

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Eleven patients with chronic ventricular arrhythmias took part in a study of N-acetylprocainamide (NAPA), the major metabolite of procainamide, in order to characterize further NAPA's clinical pharmacology and antiarrhythmic action. The frequency of ventricular arrhythmia on 24 hour ambulatory electrocardiographic recordings was comparable on recordings obtained in a prestudy screening, during treatment with placebo before administration of NAPA and after treatment with NAPA. The initial dosage of NAPA was 500 mg every 8 hours, which was increased by 500 mg increments every few days until 90 percent suppression of arrhythmia or intolerable adverse effects occurred. Only two patients achieved 90 percent suppression of ventricular ectopic complexes. The mean plasma concentration associated with 90 percent suppression of arrhythmia in these two patients was 12.6 and 32.3 mg/ml, respectively. One of these two patients was unable to continue long-term therapy with NAPA because of a rash. Other adverse effects included gastrointestinal symptoms in seven patients with visual symptoms in four patients at plasma concentrations as low as 6.9 mg/ml. NAPA obeyed linear pharmacokinetics over the range of dosages studied (500 to 2,500 mg every 8 hours) and had a half-life of 10.7 ± 1.98 hours (mean ± standard deviation). There was no change in the P-R or QRS intervals and there was a dose-dependent prolongation of the Q-Tc interval. It is concluded that in this patient group, NAPA suppressed chronic ventricular ectopic complexes without adverse effects in only a minority of patients.

N-acetylprocainamide (NAPA) is the major metabolite of procainamide in human subjects.[1] Pharmacokinetic studies have shown that this compound is well absorbed after oral dosing, is primarily eliminated by the kidneys and has a longer half-life than procainamide.[2–6] Electrophysiologically NAPA differs from procainamide in that it does not alter His-Purkinje conduction times at clinically tolerated plasma concentrations.[7,8] Preliminary studies indicate that NAPA has an antiarrhythmic action in human subjects after single[9] or multiple doses[10–12] and that long-term oral therapy is possible.[13] Evidence to date[11,13,14] indicates that long-term therapy with NAPA is less likely than procainamide to cause systemic lupus erythematosus. This study was undertaken to investigate further the antiarrhythmic activity, adverse effects and pharmacokinetics of NAPA in patients with chronic stable ventricular arrhythmias.

Methods

Study patients: Eleven patients, nine men and two women, with a mean age of 58.3 ± 11.6 years (range 42 to 75) participated in this study. Each patient had frequent and complex ventricular arrhythmias believed by their referring physician to require antiarrhythmiac therapy. The protocol was approved by the Stanford Human Subjects Committee and each patient gave written informed consent. Each patient's underlying heart disease is listed in Table I. Eight patients had documented coronary artery disease, two had presumed coronary artery disease and one patient had mitral valve prolapse. Patients with severe

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TABLE I

Clinical Characteristics of Patients

Case	Age (yr)	Diagnosis	Concurrent Medications
1	59	20 yr history PVCs	Dyazide®, vitamin E, multivitamins
2	42	MV prolapse, PVCs, COPD, angina	
3	46	CAD, s/p MI, VF × 1, PVCs	
4	68	s/p MI, CABG, PVCs, CAD	Furosemide, chlorpropamide, niacin, Aldoril®, potassium chloride
5	47	CAD, s/p MI, (VT,VF post-MI), PVCs	Aldactazide®
6	67	CAD, s/p MI, PVCs	
7	44	PVCs	Nitroglycerin
8	68	CAD, s/p MI, VT, PVCs	Spironolactone, furosemide, Surfak®
9	75	CAD, AI, PVCs, CABG	Riopan® nitropaste, furosemide, potassium chloride
10	66	CAD, s/p MI, CABG, PVCs	Maalox®
11	59	CAD, CABG, VT, VF, PVCs	Isordil,® furosemide, K-lyte,® propranolol, digoxin

AI = aortic insufficiency; CABG = coronary bypass surgery; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; MV = mitral valve; PVCs = premature ventricular complexes; s/p = status post; VF = ventricular fibrillation; VT = sustained ventricular tachycardia.

hepatic or renal disease or uncompensated congestive heart failure were excluded from this study.

Protocol design: Each patient underwent a baseline 24 hour ambulatory electrocardiographic recording to determine suitability for the study. These baseline recordings were performed with all but one patient taking no antiarrhythmic agents; the latter patient (Case 11) was taking propranolol for angina. Patients averaging at least one premature ventricular complex per minute over 24 hours were started on an initial 24 hour placebo period with one placebo tablet (identical in appearance and taste to the 500 mg NAPA tablets) taken every 8 hours. During this placebo period each patient had another 24 hour ambulatory electrocardiogram recorded. Patients were then started on 500 mg of NAPA every 8 hours and maintained on this dosage for a minimum of 3 days to allow attainment of steady state plasma drug concentrations. Each patient then underwent another 24 hour electrocardiographic recording; blood samples were taken using a heparin lock in a peripheral arm vein over an 8 hour dosing interval at the following times: immediately before administration of the drug and 30, 60, 90, 120, 180, 240, 360 and 480 minutes after each dose. An assessment of adverse effects was made for each dose by use of a standard questionnaire and by direct patient interview. Ambulatory electrocardiographic recordings were promptly processed. If there was neither a 90 percent reduction in arrhythmia compared with the frequency during the period of placebo administration nor intolerable drug adverse effects, the NAPA dose was increased by 500 mg every 8 hours (1.5 g daily) and patients were maintained on this larger dose for at least three additional days to allow attainment of new steady state plasma concentrations. Twenty-four hour ambulatory electrocardiographic recordings and blood sampling over one 8 hour dose interval were again performed. This sequence was repeated until 90 percent suppression of arrhythmia or intolerable adverse effects occurred.

Once one of these end points was reached, patients underwent blood sampling during NAPA drug withdrawal in order to measure the drug's half-life. Blood samples were obtained using a heparin lock in a peripheral vein immediately before and at the following times after the last dose of NAPA: 30, 60, 90 and 120 minutes; 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours. After drug withdrawal another ambulatory electrocardiographic recording was recorded for each patient in order to obtain a final baseline value for arrhythmia frequency without NAPA. Twelve lead electrocardiograms were obtained before entry into the study and at steady state plasma concentrations of each NAPA dose tested. These electrocardiograms were used to determine R-R, P-R, QRS and Q-T intervals (corrected for heart rate according to the Bazett formula).[15] Each patient underwent a battery of routine laboratory safety tests before and after participation in this study. Patients with greater than 90 percent reduction of frequency of ventricular ectopic complexes and without intolerable adverse effects were treated with long-term oral NAPA therapy.

Plasma concentration measurements: Five milliliters of blood was withdrawn and placed in heparinized tubes for each determination of NAPA plasma concentration. Plasma was separated by centrifugation and frozen until analysis. The plasma concentrations of NAPA were determined by a specific high pressure liquid chromatography assay modified with ion paired chromatography. Drugs were extracted from plasma into ethyl acetate after buffering with sodium bicarbonate at pH 10. The lower limit of sensitivity of the assay was 0.1 μg/ml. Mean plasma concentration over a dosing interval was determined by dividing the area under the plasma concentration time curve over one dosing interval by the duration of the dosing interval (8 hours). Half-life was determined by the log-linear least-squares best fit of the concentration versus time data between 8 and 72 hours after the last dose. To determine whether a steady state was achieved with each dose, the plasma concentrations immediately before the dose and at the end of the dosing interval were compared using a matched paired t test.

Ambulatory electrocardiographic analysis: Ambulatory electrocardiographic recordings were analyzed using the Stanford computerized ambulatory electrocardiographic analysis system.[16] This system provides an exact count of all premature ventricular complexes defined by the operator as wide QRS complexes that are premature and not preceded by apparent P wave activity. The computer classifies ectopic complexes by morphology and allows determination of the number of foci of ectopic complexes, the number of episodes of ventricular tachycardia (defined as three or more ventricular ectopic complexes in a row), the number of pairs of such complexes and the number of episodes of ventricular bigeminy occurring on a tape. The accuracy of analysis is checked individually for each tape by operator-editing of complexes in

TABLE II

NAPA Plasma Concentration Data at Various Dosages

		500 mg			1000 mg			1500 mg			2000 mg			2500 mg		
Case	$\tau_{1/2}$	Pre-Drug Cp	Peak Cp	$\overline{Cp}$	Pre-Drug Cp	Peak Cp	$\overline{Cp}$	Pre-Drug Cp	Peak Cp	$\overline{Cp}$	Pre-Drug Cp	Peak Cp	$\overline{Cp}$	Pre-Drug Cp	Peak	$\overline{Cp}$
1	—	—	—	—	11.4	14.1	11.80	14.1	22.1	17.90	23.3	30.0	25.95	—	—	—
2	—	6.45	10.26	7.86	—	—	—	—	—	—	—	—	—	—	—	—
3	9.5	2.97	5.63	4.18	5.83	8.63	6.87	8.51	15.93	12.60	—	—	—	—	—	—
4	14.0	7.19	10.20	8.09	15.66	22.50	17.74	26.01	39.51	32.32	—	—	—	—	—	—
5	10.5	4.63	9.76	6.70	9.39	17.87	13.70	15.64	22.76	18.80	20.13	37.62	25.60	23.38	40.08	32.20
6	8.0	2.61	5.74	4.31	6.70	13.28	10.47	10.72	28.26	18.43	14.93	29.76	21.93	18.62	34.98	26.90
7	10.5	2.4	4.9	3.33	5.4	9.4	7.1	9.2	14.8	12.0	15.1	23.5	18.6	—	—	—
8	—	8.4	16.8	10.36	16.7	—	—	—	—	—	—	—	—	—	—	—
9	12.5	8.3	13.7	9.8	19.0	27.0	16.0	—	—	—	—	—	—	—	—	—
10	—	6.0	10.8	8.5	11.8	19.9	15.3	21.5	36.9	28.4	—	—	—	—	—	—
11	9.9	5.3	10.7	7.2	9.4	15.7	11.2	16.4	31.1	20.0	21.6	33.0	25.0	—	—	—
Mean	10.70	5.43	9.85	7.03	10.51	16.49	12.91	15.26	26.42	20.06	17.94	30.78	23.42	21.0	37.53	29.55
SD	1.98	2.25	3.71	2.41	4.56	6.01	3.45	6.10	9.13	7.06	3.43	5.16	3.13	3.37	3.61	3.75
SEM	0.75	0.71	1.17	0.76	1.52	2.0	1.22	2.16	3.23	2.50	1.72	2.31	1.40	2.38	2.55	2.65

$\tau_{1/2}$ = half-life after drug withdrawal (hour); Cp = plasma concentration (μg/ml); $\overline{Cp}$ = mean plasma concentration over one 8 hour dose interval (μg/ml); SD = standard deviation; SEM = standard error of the mean.

each family and by sampling random minutes throughout the recording as well as minutes determined by the computer to have ectopic complexes and each type of complex ventricular arrhythmia and performing a complex by complex comparison of computer classification and operator classification. The Wilcoxon rank sum nonparametric statistical technique was used to compare the frequency of ventricular ectopic complexes on 24 hour ambulatory electrocardiographic recordings in the baseline and placebo periods and in each of these periods and the final post-study period.

Results

NAPA Plasma Concentrations

The plasma concentrations achieved for each subject on each NAPA dose are given in Table II. For each dose there was no statistically significant difference between the plasma concentration before the dose and that at the end of the dosing interval, indicating that sufficient time had elapsed during dosing to achieve steady state plasma concentrations. The mean (± standard deviation) plasma concentration immediately before the NAPA dose ranged from 5.43 ± 2.25 μg/ml for the 500 mg dose to 21.0 ± 3.37 for the two patients receiving the highest dosage of 2,500 mg every 8 hours. The peak plasma concentration occurred from 1.3 to 2.2 hours after the drug was given and ranged from 1.6 to 1.8 times the predrug "trough" level. The average plasma concentration over a dosing interval for the entire group of patients ranged from 7.03 ± 2.41 μg/ml at the 500 mg dose level to 29.6 ± 3.75 μg/ml in the two patients receiving the highest dosage. Figure 1 shows the average plasma concentration over a dosing interval as a function of administered dose for each of the nine subjects having mean plasma concentrations measured at more than one drug dose. For each patient there was an approximately linear relation between mean plasma concentration and drug dose suggesting that NAPA has linear pharmacokinetics over the range of doses studied. Half-life. (Table II) after drug withdrawal was determined in seven patients and averaged 10.70 ± 1.98 hours (range 8.0 to 14.0).

Antiarrhythmic Efficacy

Table III shows the average number of premature ventricular complexes/hour in each 24 hour ambulatory electrocardiographic recording.

Individual patient responses. Table IV shows the percent change in frequency of ventricular ectopic complexes for each NAPA dose in each patient compared with the frequency in the pre-NAPA placebo period. Only two patients achieved 90 percent reduction in frequency of ectopic complexes used to define indi-

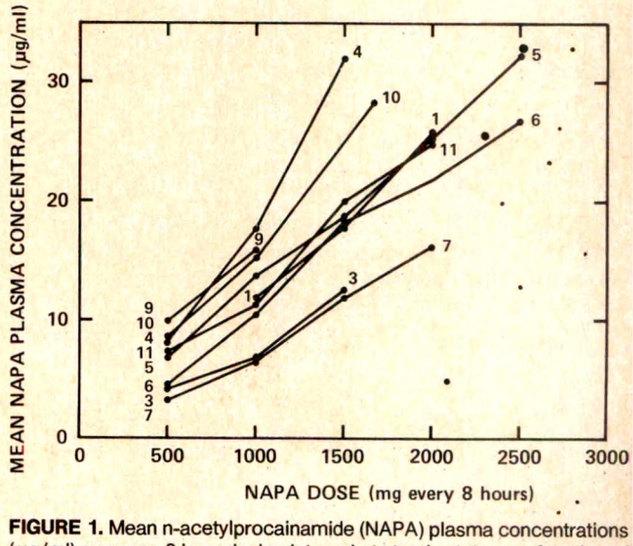

FIGURE 1. Mean n-acetylprocainamide (NAPA) plasma concentrations (μg/ml) over one 8 hour dosing interval at steady state as a function of NAPA dose for all patients with data at more than one dose level. Note the approximate linear relation between plasma concentration and dose for each patient. Note also the approximate three-fold range of inter-subject variation of plasma concentrations for any given dose.

TABLE III

Average Hourly Frequency of Premature Ventricular Complexes (PVCs) for Each Patient on Each NAPA Dose

			NAPA					
Case	Base line	Placebo	500 mg	1000 mg	1500 mg	2000 mg	2500 mg	Post NAPA
1	824	1064	—	697	314	358	—	371
2	104	630	453	—	—	—	—	—
3	60	8.2	3.5	5.4	0.33	—	—	15.4
4	380	470	265	64	33	—	—	551
5	541	559	736	550	311	187	266	129
6	417	343	516	412	330	213	274	326
7	864	1678	598	795	833	852	—	1345
8	1186	1081	877	737	—	—	—	—
9	75	184	172	229	—	—	—	228
10	62	195	198	126	262	—	—	202
11	210	232	188	284	168	312	—	328
Mean	429	586	400	390	281	384	270	388
SD	385	502	281	292	257	271	6.72	390
SEM	116	151	89	82	91	121	4.75	130

idual responders to NAPA. In one of these patients (Case 4) the reduction was definitely considered a result of treatment with NAPA. The reduction in ventricular ectopic complexes was dose-dependent, with a 93 percent decrease achieved with the dosage of 1,500 mg every 8 hours and return of the ectopic complexes in the post-NAPA 24 hour recording. Unfortunately this patient was unable to continue on long-term therapy because of a severe rash.

Patient 3 also had a greater than 90 percent reduction of ectopic complexes with NAPA, achieving a 93 percent decrease with the 1,500 mg dose level of NAPA. However, it was initially not clear that this represented a true drug response because the patient had shown an 86 percent spontaneous reduction (from 60 to 8.2/hour) in arrhythmia frequency between the placebo and initial baseline recordings. After 1,500 mg dosage of NAPA was withdrawn, the ectopic complex frequency increased to 15.37/hour, then decreased to almost 0 with reinstitution of NAPA. On the basis of this finding the patient was considered a NAPA responder and has subsequently been receiving maintenance therapy with the drug for more than 1 year. He has continued to show almost no ectopic complexes on sequential ambulatory electrocardiographic recordings, has had a marked reduction in symptoms of palpitations and has maintained a negative fluorescent antinuclear antibody test. The NAPA plasma concentration associated with 90 percent reduction in these two patients was, respectively, 12.6 (Case 3) and 32.3 (Case 4) μg/ml.

TABLE IV

Percent Change in Frequency of Premature Ventricular Complexes on 24 hour Ambulatory Recording for Each Patient on Each NAPA Dose Compared With Electrocardiographic Frequency While Taking Placebo

	NAPA					
Case	500 mg	1000 mg	1500 mg	2000 mg	2500 mg	Post NAPA
1		−35%	−70%	−67%		−65%
2	−28%					
3	−57%	−34%	−96%			+87%
4	−44%	−86%	−93%			+17%
5	+32%	−2%	−44%	−67%	−52%	−77%
6	+5%	+20%	−4%	−38%	−20%	−5%
7	−64%	−53%	−50%	−49%		−20%
8	−19%	−32%				
9	−6%	+25%				+21%
10	+1%	−35%	+34%			+3%
11	−19%	+22%	−28%	+34%		+42%

Group responses: The average number of ventricular ectopic complexes/hour during the initial baseline recording was 429 ± 385. This value is not statistically significantly different from the 586 ± 501/hour recorded during the pre-NAPA placebo period. Nine patients underwent repeat ambulatory monitoring after withdrawal of NAPA therapy and had an average of 388 ± 390 complexes/hour. This number was not statistically significantly different from that in the baseline and placebo recordings. Thus there did not appear to be a significant trend toward an increase or decrease in average frequency of ventricular arrhythmia in this group of patients during the course of this study.

Ten patients received the 500 mg dose and 10 received the 1,000 mg dose every 8 hours. There was no statistically significant reduction of ventricular ectopic complexes with either dose (average hourly frequency of ectopic complexes of 400 ± 281 and 390 ± 292, respectively). Because of the high incidence of adverse effects fewer numbers of patients received the 1,500, 2,000, and 2,500 mg doses of NAPA. There did not seem to be a readily apparent group reduction in ectopic complex frequency in patients tolerating the larger doses (Table III). Examining ventricular ectopic frequency as a function of plasma concentration rather than of dose showed a slight trend toward suppression at concentrations above 24 μg/ml (Fig. 2). Just as the total number of ventricular ectopic complexes did not seem to be markedly reduced for the group, complex forms of ectopic complexes (quantitatively described as number of episodes of pairs, runs and bigeminy and

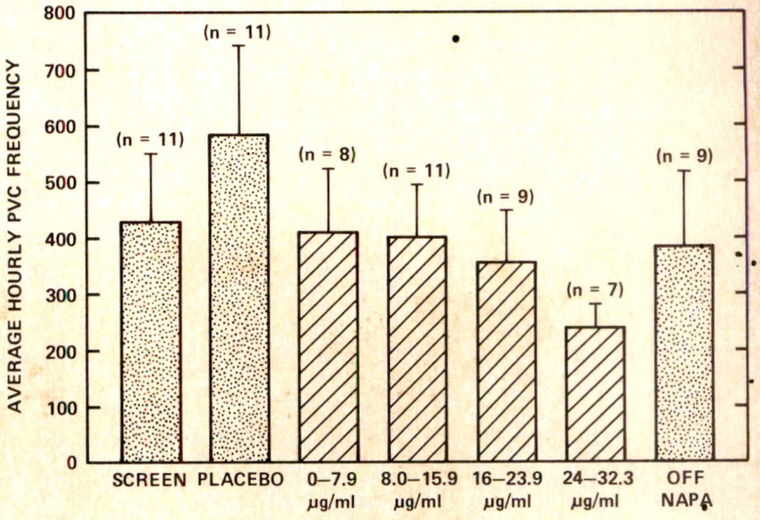

FIGURE 2. Average hourly frequency of premature ventricular complexes (PVC) (± standard error of the mean) seen on ambulatory electrocardiographic recordings on the initial screening test, during the predrug placebo period, during therapy with NAPA at various doses and at the end of the study after withdrawal of NAPA. Shown also are the group average serum concentration-response data for NAPA. Although there was a suggestion of a reduction of ventricular arrhythmias above a concentration of 24 μg/ml the decrease was not striking. n = the number of 24 hour recordings in each category.

number of morphologies present on each 24 hour recording) were not greatly affected by therapy with NAPA.

Electrocardiographic Findings

Table V summarizes the average interval measurements in the 12 lead electrocardiogram made on each dose of NAPA. There were no significant changes in P-R or QRS intervals. There was a suggestion of a dose-dependent prolongation of the R-R interval from 840 ± 155 ms in the control recording to 900 ± 109 ms with the dose of 2,000 mg. Although this trend in cycle length was noted for the averaged group data, it was not readily apparent for any individual patient. There was a definite dose-dependent prolongation of the Q-Tc interval for both individual patients as well as for the group average (Fig. 3). One patient had an intraventricular conduction defect and another had intermittent right bundle branch block before NAPA therapy and neither had these abnormalities worsened with NAPA.

Adverse Effects

Adverse gastrointestinal effects occurred most frequently (7 of the 11 patients). Most patients described a sensation of nausea or a "queasy" stomach with one subject also vomiting and two others having associated diarrhea. Several patients initially had mild gastrointestinal symptoms, but with larger drug doses the adverse effects worsened in all cases. The mean plasma concentration associated with the onset of gastrointestinal symptoms in these seven patients was respectively, 6.9, 7.9, 8.5, 18.4, approximately 20 to 22, 25 and 25.6 μ/ml.

Four patients complained of visual symptoms including "blurred" vision (three patients) and "flashes" or "wavy" vision (one patient). The latter subject was noted to have bilateral vitreous detachments without permanent sequellae. Although two independent consultant ophthalmologists did not believe that the latter patient's symptoms were due to NAPA, we cannot fully exclude that possibility.

One patient (Case 4) experienced an allergic reaction that was believed to be due to NAPA. This patient had the most striking antiarrhythmic response to NAPA and was to have received long-term oral therapy with the drug. After 15 days of NAPA therapy he exhibited a diffuse pruritic urticarial rash that was most prominent over his trunk and buttocks. Administration of the drug was stopped immediately, and the rash promptly resolved. Because there was modest circumoral edema it was decided not to rechallenge the patient. A careful history revealed no other potential cause for the rash.

One patient died while taking part in this study. He was a 68 year old man with coronary artery disease and

TABLE V

Average (±standard deviation) Electrocardiographic Intervals for Each NAPA Dose

		NAPA Dose				
	Control	500 mg	1000 mg	1500 mg	2000 mg	2500 mg
	(n = 10)	(n = 9)	(n = 9)	(n = 8)	(n = 4)	(n = 2)
P-R (s)	0.163 ± 0.030	0.151 ± 0.023	0.161 ± 0.024	0.164 ± 0.013	0.158 ± 0.013	0.150 ± 0.028
QRS (s)	0.085 ± 0.016	0.080 ± 0.012	0.086 ± 0.017	0.086 ± 0.018	0.080 ± 0.022	0.080 ± 0.028
R-R (ms)	840 ± 155	862 ± 129	879 ± 87	879 ± 75	900 ± 109	877 ± 67
Q-T_c (s)	0.433 ± 0.038	0.463 ± 0.038	0.477 ± 0.026	0.485 ± 0.032	0.498 ± 0.025	0.505 ± 0.0071

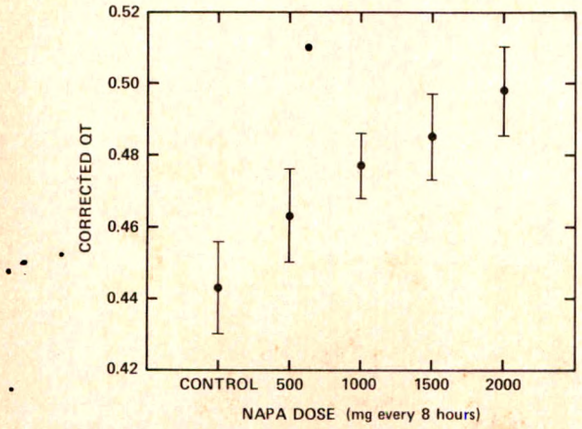

FIGURE 3. Average Q-Tc interval (± standard error of the mean) as a function of the dose of NAPA. This dose-dependent Q-Tc prolongation was also seen in each individual patient.

moderately well compensated congestive heart failure. He had a long history of complex ventricular arrhythmia including frequent brief runs of ventricular tachycardia causing palpitation but never dizziness or syncope. He had no change in his arrhythmias or marked change in the Q-T interval with the 500 or 1,000 mg dose of NAPA. After 3 days on the 1,500 mg dose he died suddenly without experiencing any untoward symptoms. It seems most likely that his death was related to his underlying heart disease. Although NAPA clearly failed to prevent his death, there is no compelling reason to suspect that it contributed to it, although we cannot exclude that possibility.

Discussion

Our experience with n-acetylprocainamide (NAPA) in this protocol was disappointing. We were able to achieve 90 percent suppression of ventricular ectopic complexes in only 2 of 11 patients. We chose 90 percent reduction of ventricular ectopic complexes in order to avoid the possibility of classifying a spontaneous decline of ventricular arrhythmias as a response to NAPA.[17,18] Lowering our criterion for defining drug responders to as low as 70 percent reduction would have had little effect on the overall results of this study. Whereas the patient group studied did include patients referred because their arrhythmias were difficult to suppress with more standard agents, it is not dissimilar from that which we have utilized for other antiarrhythmic drug studies.[19–21] In fact, several patients unsuccessfully treated with NAPA have subsequently had arrhythmias successfully suppressed with other new compounds.

Comparisons with previous studies: Superficially, our experience with NAPA seems less encouraging than that reported from other centers. Lee et al.[9] reported on the antiarrhythmic response to a single oral dose of 1.5 g of NAPA. They concluded that six of nine patients responded to NAPA. However, three of these six had very transient reductions in the frequency of ventricular ectopic complexes, which could have been due to spontaneous variations. Only three of the nine had a marked and sustained suppression of the type one must observe during acute drug testing to be confident of drug effect.[22] Atkinson et al.[10] performed a NAPA dose-ranging study in 10 patients with chronic ventricular ectopic complexes. Only four patients achieved greater than 80 percent reduction in a 6 hour electrocardiographic recording and one of these had no return of ectopic complexes after administration of the drug was stopped. Woosley et al.[11] found that only 7 (32 percent) of 22 patients had reproducible reduction of ventricular ectopic complexes with NAPA at plasma concentrations ranging from 8 to 18 μg/ml. Kluger et al.[12] found that 9 of 15 patients had a greater than 50 percent reduction of ventricular ectopic complexes in a 24 hour electrocardiographic recording. The use of a 50 percent reduction response criterion suggests that the actual number of true drug responders may have been less than nine.[18] Taken as a whole, these studies, when combined with ours, suggest that approximately one third of patients may be expected to have significant suppression of ventricular ectopic complexes while taking oral NAPA.

Adverse effects: Other studies have reported adverse effects from NAPA similar to those found in our study. Atkinson et al.[10] found that 40 percent of patients had adverse effects during a brief dose-ranging period. These effects included nausea, anorexia, emesis, diarrhea and insomnia. Kluger et al.[12] noted 44 percent of patients to have adverse effects. The higher incidence of such effects in our study was in part due to the protocol design that called for increasing the dose of NAPA until either adverse effects or 90 percent reduction of premature ventricular complexes occurred. However, in several instances we observed side effects at plasma concentrations of less than 10 μg/ml. For NAPA it seems that there is considerable overlap between plasma concentrations at which side effects occur and those at which antiarrhythmic efficacy is observed. Thus it would be expected that many of the patients who do have antiarrhythmic response to NAPA might not be able to continue long-term therapy because of adverse effects.

Electrophysiologic effects: The observations that NAPA prolonged the Q-Tc interval but did not alter the P-R interval and QRS duration and that the condition of patients with abnormalities of His-Purkinje conduction did not worsen during NAPA therapy are compatible with the drug's known electrophysiologic action. In isolated Purkinje fibers[23] the drug does not alter the phase 0 upstroke or phase 4 depolarization but does prolong action potential duration. In both dogs[7] and human beings[8] we have shown that intravenous NAPA has no consistent effect on intraventricular or His-Purkinje conduction times but does prolong ventricular refractoriness and Q-T intervals. The lack of action on His-Purkinje conduction at clinically tolerated plasma concentrations makes the drug electrophysiologically different from procainamide.

Pharmacokinetics: Our study demonstrates that NAPA obeys linear pharmacokinetics over the clinically

tolerated range of oral doses. Thus, for any change in the dose of NAPA there will be an equivalent proportional change in steady state plasma concentration. The average half-life of 10.7 hours in our study is longer than the half-life of 6.2 hours reported by Atkinson et al. in normal subjects[5] but similar to the half-life of 10.9 hours they found in patients with ventricular arrhythmias.[10]

Therapeutic implications: The data from our and other studies of NAPA have implications for the use of oral procainamide. The different electrophysiologic actions of procainamide and NAPA imply that antiarrhythmic response to one compound will not guarantee response to the other, a finding recently confirmed in human subjects by Woosley et al.[11] Because significant antiarrhythmic effect is not consistently observed in patients receiving NAPA and may occur only at NAPA plasma concentrations higher than those usually occurring during long-term dosing with procainamide (in subjects without renal failure), the antiarrhythmic action of NAPA may have little to do with the antiarrhythmic response observed during long-term therapy with procainamide. Certainly one cannot advise patients to take procainamide less frequently than every 4 hours or to omit doses of procainamide in the middle of the night with the expectation that NAPA will provide continuing antiarrhythmic action after procainamide plasma concentrations are subtherapeutic. Although many laboratories are now reporting procainamide and NAPA plasma concentrations, for most patients the clinical value of knowing the NAPA concentration would seem to be minimal. In any patient one could not predict whether NAPA and procainamide might have antiarrhythmic actions that are synergistic, competitive or bear no relation to one another. Finally, it seems likely that some of the adverse gastrointestinal effects seen during oral procainamide therapy may result from NAPA rather than from procainamide. This would be most likely to occur during administration of large doses of procainamide or in patients with renal impairment in whom high NAPA levels may occur[3,4] but occasionally might occur in rapid acetylators receiving standard doses of procainamide.

The ultimate role of NAPA remains to be defined. Whereas it clearly has antiarrhythmic actions in some patients with ventricular arrhythmias, in our experience it seems less effective than other available and investigational drugs for suppression of ventricular ectopic complexes. Its high rate of adverse effects would seem to be a drawback to its widespread clinical use. Because it is not a direct substitute for procainamide, much of the value of its lack of induction of systemic lupus erythematosus seems to be lost because patients responsive to procainamide cannot necessarily be switched successfully to NAPA. Its long half-life permits a reasonable dose interval and its lack of effect on the cardiac conduction system may offer some advantages in patients with atrioventricular nodal or His-Purkinje disease. The drug's reported lack of myocardial depressant effect[10] may also have advantages in patients with compromised ventricular function. Finally it should be recognized that studies to date have only evaluated NAPA's antiarrhythmic effect in one model for new drug evaluation, namely, the suppression of chronic asymptomatic or only moderately symptomatic ventricular arrhythmias. The compound needs further evaluation in patients with recurrent sustained ventricular tachycardia or ventricular fibrillation where antiarrhythmic action may possibly be independent of the suppression of isolated ventricular ectopic complexes.

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Mexiletine For Refractory-Ventricular Arrhythmias: Results Using Serial Electrophysiologic Testing

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Mexiletine was administered during serial drug testing to 35 patients with electrically inducible ventricular arrhythmias and to 6 with recurrent ventricular tachycardia that could not be induced or terminated by programmed cardiac stimulation. All patients had arrhythmias resistant to all conventionally available agents. Electrically induced arrhythmias were completely suppressed during mexiletine therapy in 13 patients. In 12 patients no antiarrhythmic regimen was completely suppressive and in 7 of these mexiletine favorably modified the response to programmed stimulation. In four of six patients with frequent episodes of spontaneous ventricular tachycardia that were not inducible by programmed cardiac stimulation, arrhythmia was controlled by mexiletine. The presence of complete arrhythmia suppression with mexiletine during acute testing accurately predicted long-term freedom from recurrent arrhythmia in 16 of 17 patients over a mean follow-up period of 12.6 ± 6 months. Severe adverse neurologic effects were noted early during mexiletine therapy in three patients, but no patient discharged on such therapy experienced major adverse effects. The study demonstrates that mexiletine can provide well tolerated effective prophylaxis against recurrent ventricular arrhythmias in a significant proportion of patients resistant to conventional drugs.

Mexiletine, 1-(2′,6′-dimethylphenoxy)-2-aminopropane, a primary amine structurally resembling lidocaine with anticonvulsant, antiarrhythmic and antifibrillatory properties, is currently under investigation in the United States for use in the treatment of ventricular arrhythmias. The drug has been demonstrated to be effective in preventing ventricular arrhythmias associated with acute myocardial infarction[1–3] as well as in a variety of other clinical settings.[4–7] These studies have reported an acceptable toxic to therapeutic ratio and pharmacokinetic properties that allow for convenient dosage regimens. The drug's potential role in the treatment of life-threatening ventricular arrhythmias has not been fully defined.

We and other groups[8–11] have found that patients with a history of either ventricular tachycardia or ventricular fibrillation frequently manifest reproducible ventricular arrhythmias in response to programmed electrical stimulation of the heart. The ability of a drug to suppress induction of tachycardia during such stimulation has been shown to predict antiarrhythmic efficacy.[8–11] In this report, we review our experience with the use of electrophysiologic techniques to assess the antiarrhythmic efficacy of mexiletine in 41 patients with life-threatening ventricular arrhythmias that were unresponsive to all conventionally available antiarrhythmic agents.

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TABLE I

Patient Characteristics

Case	Age (yr) & Sex	Diagnosis/ Arrhythmia	Initial Electrophysiologic Study: Arrhythmia (rate)	Initial Electrophysiologic Study: Initiation	Initial Electrophysiologic Study: Termination	Electrophysiologic Study on Mexiletine: Alone	Electrophysiologic Study on Mexiletine: With (2nd Agent)	Final Therapy (mg)	Follow-Up (mo)
A. Patients With Inducible Arrhythmias									
1	69 F	CAD/VT	SusVT (170)	VPS	RVP	SusVT (220)	—	PA 500 q3h*; DP 150 q6h	24
2	66 M	CAD/VT	SusVT (170) (on PA)	VPS, RVP	RVP	SusVT (215)	—	Amio 800 qd	19
3	49 M	VHD/VT	SusVT (210)	VPS, RVP	CV	SusVT (180)	—	Hospital death	—
4	59F	CAD/VT	SusVT (200)	VPS, RVP	CV	—	SusVT (200 (with Quin)	Anx/See; hospital death	—
5	71M	CAD/VT	SusVT (160)	VPS	RVP	—	SusVT (110) (with Quin,PA)	Mex 300 q6h*; Quin 330 q6h; PA 500 q4h	5†
6	68M	CAD/VT	SusVT (200)	RVP	CV	NT (tremor)	—	CABG, DP 100 q8h; PH 100 q8h	26
7	56M	CAD/VT	SusVT (175)	VPS, RVP	RVP	SusVT (130)	SusVT (110) (with Quin)	Mex 300 q6h*; Quin 330 q12h; RFP	17
8	64M	CAD/VT	SusVT (200)	RVP	RVP	SusVT (200)	No VT (with PA)	Mex 200 q6h; PA 375 q4h	12†
9	72F	CAD/VT	SusVT (150)	RVP	RVP	NT spont VT	—	Quin 330 q4h*; PA 500 q4h	14
10	55M	CAD/VT	NSVT (240)	VPS	Spont	SusVT (260)	—	Amio 800 qd	19
11	50M	CCM/VT	SusVT (230)	VPS, RVP	RVP	No VT	—	Mex 200 q6h	15
12	62M	CAD/VT	NSVT (215)	VPS, RVP	Spont	No VT	—	Mex 200 q6h	15†
13	56M	CAD/VT	SusVT (180); (on PA, Quin, IABP)	VPS	RVP	No VT	—	Mex 300 q6h	10
14	48M	CAD/VT	SusVT (180)	VPS	CV	NT (spont VT)	—	Anx/See; NAD	9
15	50M	CAD/VT	SusVT (165) (on DP)	VPS	RVP	—	No VT (with DP)	MEX 200 q6h; DP 200 q6h	9
16	70M	CCM/VT	NSVT (150)	VPS, RVP	Spont	NT (tremor)	—	Amio 800 qd*	8
17	61M	CAD/VT	SusVT (240) (on Quin)	RVP	LIDO	NT (spont VT)		Amio 800 qd*	7
18	64M	CAD/VT	SusVT (130)	RVP	CV	SusVT (105)	—	Mex 250 q6*	5

continued on next page

TABLE I (continued)

Patient Characteristics

Case	Age (yr) & Sex	Diagnosis/ Arrhythmia	Initial Electrophysiologic Study: Arrhythmia (rate)	Initial Electrophysiologic Study: Initiation	Initial Electrophysiologic Study: Termination	Electrophysiologic Study on Mexiletine: Alone	Electrophysiologic Study on Mexiletine: With (2nd Agent)	Final Therapy (mg)	Follow-Up (mo)
A. Patients With Inducible Arrhythmias									
19	65M	CAD/VT	NSVT (220)	VPS	Spont	NSVT (230)	—	Amio 600 qd	5
20	56M	CAD/VT	VT (120)	VPS, RVP	RVP	NT (spont VT)	—	NAPA 1500 q8*	3
21	53M	CAD/VT	NSVT (250)	VPS, RVP	Spont	NSVT (240)	No VT (with DP)	Mex 200 q6h; DP 100 q6h	14
22	54M	CAD/VT	NSVT (240)	VPS, RVP	Spont	3 RVR	—	Mex 200 q6h*	6†
23	74M	CAD/VT	RVR	VPS	Spont	No RVR	—	Mex 200 q6h	13
24	67F	CAD/VF	SusVT (195)	RVP	RVP	No VT	—	Mex 200 q6h	12
25	70M	CAD/VF	NSVT (245)	VPS, RVP	Spont	NSVT (260)	No VT (with Quin)	Mex 200 q6h; Quin 300 q6h	17
26	53M	CAD/VF	NSVT (240)	VPS, RVP	Spont	NT (spont VT)	—	Amio 1000 qd; Quin 600 q6h	12
27	59M	CAD/VF	RVR	RVP	Spont	No RVR	—	Mex 200 q6h	24
28	42F	CAD/VF	NSVT (260)	VPS	Spont	No VT	—	Mex 200 q6h	10
29	52M	CAD/VF	VF	VPS	CV	NSVT (250)	—	CABG,NAD	6
30	73F	CAD/VF	SusVT (240)	VPS	CV	No VT	—	Mex 200 q6h	5
31	65M	VHD/VF	SusVT (185)	VPS	CV	NSVT (220)	SusVT (145) (with PA)	Mex 300 q6h*; PA 500 q4h	5
32	54M	CAD/VF	SusVT (160)	VPS	RVP	SusVT (160)	—	Amio 800 qd	5
33	59M	CAD/VF	SusVT (215)	VPS	RVP	SusVT (190)	—	Mex 200 q6h*	5
34	67M	CAD/VF	SusVT (240)	VPS	CV	SusVT (250)	—	Mex 300 q6h*	4
35	54M	CAD/VF	RVR	VPS, RVP	Spont	No RVR	—	Mex 200 q6h	3
B. Patients Without Inducible Arrhythmias									
36	70F	CAD/VT	Not inducible			No VT‡	—	Mex 200 q8h	18
37	23F	VHD/VT	Not inducible			No VT‡	—	Mex 200 q8h	16
38	47F	VHD/VT	Not inducible			No VT‡	—	Mex 300 q8h	20
39	82M	CAD/VT	Not inducible			No VT‡	—	Hospital death	—
40	53M	NSHD/VT	Not inducible			VT‡	—	Prop 40 q8h	11
41	59M	NSHD/VT	Not inducible			No VT‡	—	Mex 300 q6h; Quin 200	1

* Arrhythmia still inducible on final regimen. † Late death. ‡ Results of ambulatory monitoring with patient receiving mexiletine.

Amio = amiodarone; Anx/See = aneurysmectomy and subendocardial excision; CABG = coronary bypass grafting; CAD = coronary artery disease; CCM = congestive cardiomyopathy; CV = cardioversion; d = day; DP = disopyramide; h = hour; IABP = intraaortic balloon pumping; LIDO = lidocaine; NAD = no antiarrhythmic drugs; NAPA = N-acetylprocainamide; NSHD = no structural heart disease; NSVT = nonsustained ventricular tachycardia; NT = not tested; PA = procainamide; PH = phenytoin; Prop = propranolol; q = every; Quin = quinidine; RFP = patient-activated radiofrequency pacemaker; RVP = rapid ventricular pacing; RVR = repetitive ventricular responses; Spont = spontaneous; SusVT = sustained ventricular tachycardia; VF = ventricular fibrillation; VHD = valvular heart disease; VPS = ventricular premature stimuli; VT = ventricular tachycardia.

Methods

Study patients: We administered mexiletine to 41 patients with a history of recurrent ventricular tachycardia or ventricular fibrillation who had failed drug trials with all conventionally available antiarrhythmic agents. We defined a prior drug failure either as (1) an episode of symptomatic ventricular tachycardia or ventricular fibrillation occurring at a time when the plasma concentration of the antiarrhythmic agent was within the accepted therapeutic range, (2) an unacceptable toxic effect, or (3) the ability to induce a ventricular arrhythmia in the presence of adequate plasma concentration of the agent. All patients had been referred to the clinical electrophysiology laboratory of this hospital for comprehensive evaluation and prescription of antiarrhythmic therapy. The group consisted of 32 men and 9 women with a mean age of 56 years. Twenty-six patients had had recurrent ventricular tachycardia and 15 had had one or more episodes of ventricular fibrillation. All patients whose presenting arrhythmia had been associated with an acute myocardial infarction were excluded from this study. The primary cardiac diagnoses are listed in Table I.

Initial electrophysiologic studies: These studies were performed with the patient in a fasting, nonsedated state after informed consent had been given. Administration of antiarrhythmic drugs was discontinued at least 48 hours before the study in all but four patients. Digitalis, if required for heart failure or atrial fibrillation, and propranolol, if required for angina, were maintained at constant dosage throughout the period of study. Three quadripolar electrode catheters with a 1 cm interelectrode distance were inserted percutaneously through femoral and antecubital veins and positioned under fluoroscopic guidance at multiple intracardiac sites. Catheter positions in all patients included the lateral right atrium, the atrioventricular junction for recording electrical activity from the bundle of His, and the right ventricular apex. The distal pair of electrodes on each catheter was used for stimulation and the proximal pair for recording local electrograms. Intracardiac recordings were filtered at 30 to 500 hertz and displayed simultaneously with surface electrocardiographic leads I, II and V_1 on a multichannel oscilloscope (Electronics for Medicine VR-12). Data were stored on frequency modulated magnetic tape (A. R. Vetter Co.) and later retrieved on photographic paper at speeds of 100 to 200 mm/s.

Cardiac stimulation was performed with a programmable constant current stimulator (Medtronic 5325) that delivered rectangular pulses of 2 ms duration. All ventricular stimulation was carried out from the right ventricular apex at twice diastolic threshold. The following stimulation protocol was used:

1. Atrial pacing at rates from 100 to 300 beats/min.
2. Premature atrial stimulation during atrial pacing at one or more basic cycle lengths.
3. Ventricular pacing at rates from 60 to 150 beats/min for 30 seconds.
4. Premature ventricular stimulation with single (S_2) and double (S_2-S_3) extrastimuli during sinus rhythm and during fixed rate atrial and ventricular pacing after every eighth paced beat at multiple basic cycle lengths (S_1-S_1).
5. Rapid ventricular pacing at rates from 150 to 280 beats/min. Pacing bursts of 2 to 5 beats were delivered at progressively shorter cycle lengths until 1:1 ventricular capture could no longer be achieved, a ventricular arrhythmia occurred or a paced rate of 280 beats/min was reached.
6. If sustained ventricular tachycardia was initiated, bursts of rapid ventricular pacing at rates between 150 and 300 beats/min were applied in an attempt to terminate the arrhythmia. If ventricular fibrillation occurred or if ventricular tachycardia resulted in loss of consciousness, external electrical cardioversion was performed immediately.

Definitions: Sustained ventricular tachycardia was defined as ventricular tachycardia that persisted for at least 100 beats and required pacing, electrical cardioversion or drug administration for termination. Ventricular tachycardia was defined as nonsustained if it persisted for at least 5 beats and reverted spontaneously to the original rhythm within 100 beats. We considered repetitive ventricular responses significant only if they were 3 or 4 beats in length, could be reproducibly initiated, and were not due to His-Purkinje reentry. The stimulation protocol was carried to conclusion except in those patients who required external direct current countershock for termination of ventricular tachycardia or fibrillation.

Serial electrophysiologic testing during oral drug treatment: In the patients in whom programmed cardiac stimulation elicited a ventricular arrhythmia, an indwelling right ventricular apical pacing electrode was inserted percutaneously through a subclavian or antecubital vein and used to carry out serial electrophysiologic testing after 48 hours of therapy on each of a variety of oral drug regimens. The stimulation protocol employed was identical to that described except that atrial stimulation was not performed. Complete suppression of the ability to initiate a ventricular arrhythmia by programmed stimulation was the desired final end point (Fig. 1). If no antiarrhythmic regimen tested produced this result, the patient either underwent a cardiac surgical procedure, died in the hospital or was discharged on the antiarrhythmic regimen that had either maximally slowed or abbreviated the ventricular tachycardia or made it most difficult to induce during serial electrophysiologic testing. Therapy selected on the basis of these latter criteria was referred to as being partially suppressive.

Mexiletine protocol: Patients whose tachycardias were not inducible during programmed stimulation underwent a trial of mexiletine therapy during continuous ambulatory electrocardiographic monitoring for at least 4 consecutive 24 hour periods. Total abolition of all episodes of ventricular tachycardia with reappearance of the arrhythmia after discontinuation of mexiletine therapy was the criterion for complete suppression in this group.

Mexiletine was administered as a 400 mg loading dose followed by 400 to 1,200 mg daily in three or four divided doses. Because mexiletine plasma concentrations were not routinely available, the dosage in each patient was titrated upward until either a satisfactory response, a 1,200 mg daily dosage, or dose-related toxicity occurred. Serial electrophysiologic testing was performed as described. Except in two cases, combinations of other drugs with mexiletine were used only if the patient had failed to respond to each of the agents separately.

Results

Electrophysiologic observations: The essential clinical data and electrophysiologic observations for the 41 patients are presented in detail in Table I. Twenty of 26 patients with recurrent ventricular tachycardia and all 15 patients with prior ventricular fibrillation had electrically inducible ventricular arrhythmias. The mean rate of the induced tachycardias was 200 ± 37 (mean ± standard deviation) beats/min. Because of the reproducible modes of initiation and termination of these tachycardias, they were considered to be most probably due to reentry.[12,13] The remaining six patients, all of whom had had recurrent ventricular tachycardia,

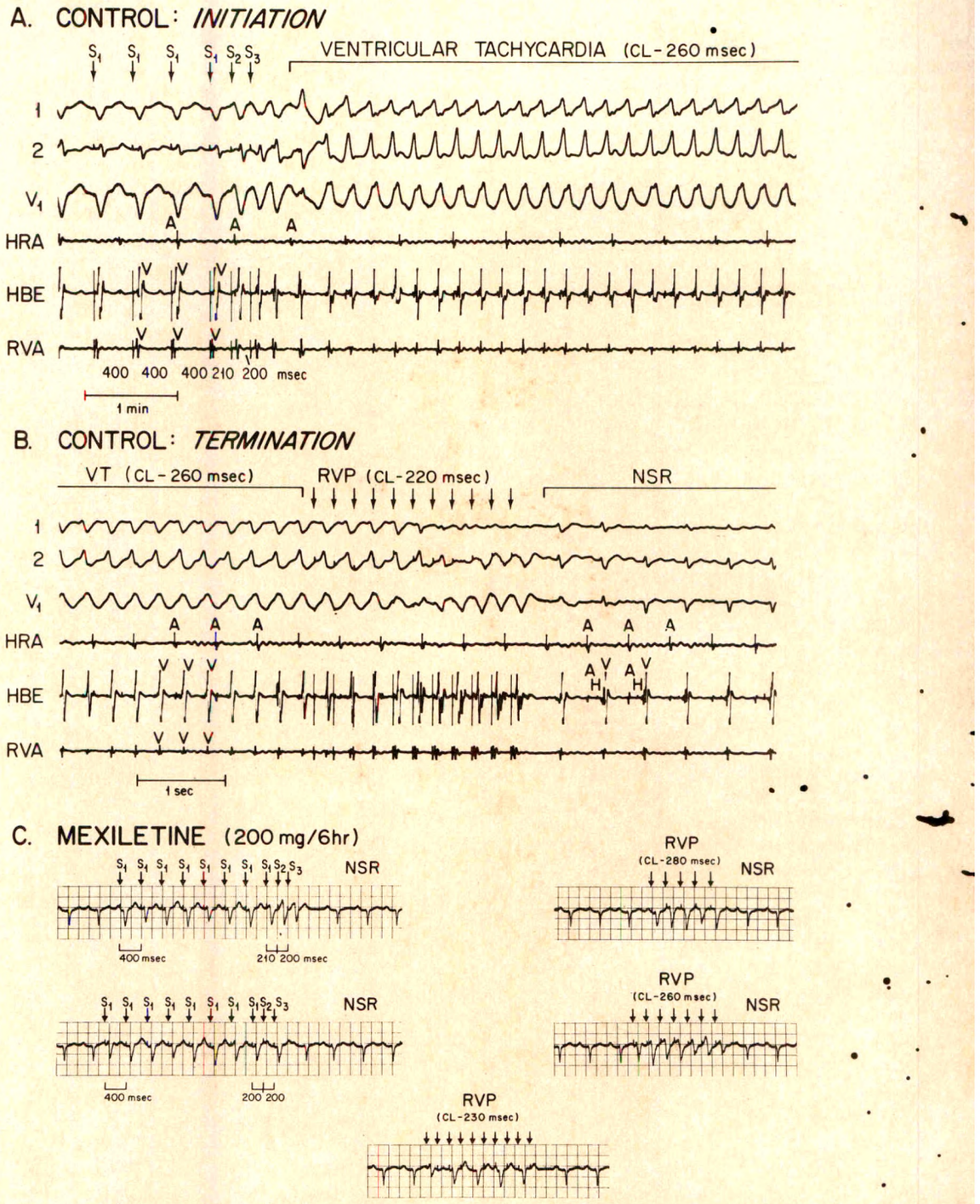

FIGURE 1. Case 11. Serial electrophysiologic testing in a patient with recurrent ventricular tachycardia. Panels **A** and **B** illustrate initiation and termination of ventricular tachycardia during control electrophysiologic studies while the patient was taking no antiarrhythmic drugs. In both panels, the tracings (**from top to bottom**) represent surface electrocardiographic leads I, II and V_1, a high right atrial electrocardiogram (HRA), a His bundle electrocardiogram (HBE) and a right ventricular apical electrocardiogram (RVA). In **A,** two sequential premature ventricular depolarizations (S_2 and S_3) delivered during fixed rate ventricular pacing (S_1 and S_1) result in the initiation of sustained ventricular tachycardia identical to that observed clinically. In **B,** the induced ventricular tachycardia (VT) is terminated by a burst of rapid ventricular pacing (RVP). **C** illustrates failure to initiate ventricular tachycardia in the same patient 48 hours after the initiation of therapy with oral mexiletine. All electrocardiograms in this panel represent lead II. The first tracing illustrates ventricular pacing and premature ventricular stimulation at cycle lengths and coupling intervals identical to those in panel **A** that reliably and reproducibly initiated ventricular tachycardia with the patient taking no drugs. The second electrocardiogram illustrates the effective refractory period of the right ventricular muscle encountered by the first premature ventricular stimulus (S_2). Premature ventricular stimulation with single (S_2) and double (S_2-S_3) stimuli over a full range of coupling intervals at multiple basic cycle lengths (S_1-S_1) failed to initiate ventricular tachycardia in the presence of mexiletine. The subsequent tracings (**on right**) illustrate bursts of rapid ventricular pacing at progressively shorter cycle lengths until only 2:1 capture of the ventricle occurs. Note failure of these bursts to initiate ventricular tachycardia. CL = cycle length; NSR = normal sinus rhythm.

TABLE II

Response to Mexiletine: Dependence on Rate of Induced Tachycardia (29 Patients*)

<185 beats/min (CL >325 ms, 155 ± 20 beats/min†)	
Complete suppression	0/8‡
Partial suppression	3/8
>185 beats/min (CL ≤325 ms, 230 ± 22 beats/min)	
Complete suppression	11/21‡
Partial suppression	4/21

* The four patients studied initially during treatment with another antiarrhythmic drug and the two patients with early neurologic toxicity are excluded. † Mean value ± standard deviation. ‡ p = 0.01 by Fisher's Exact Test.

had no electrically inducible tachycardias. The spontaneously occurring tachycardias in these patients exhibited a wide range of coupling intervals to the underlying rhythm at initiation, could be suppressed by supraventricular or ventricular overdrive with reappearance after cessation of the overdriving stimuli, and were not initiated by critically timed spontaneous premature beats. Because we have found the right ventricular apex to be the only suitable site for catheter placement during serial drug trials, we did not attempt stimulation at other ventricular sites. The electrophysiologic mechanism for the tachycardias in these six patients remains uncertain[12,13] and the arrhythmias are, henceforth, referred to as noninducible tachycardias.

Response to mexiletine: *Patients with inducible ventricular arrhythmias:* Thirteen of the 35 patients with electrically inducible ventricular arrhythmias manifested complete suppression of their ventricular tachycardia while receiving mexiletine either alone (9 patients) or in combination with a second agent that had previously been ineffective when used alone (4 patients). In 12 of the remaining 22 patients, inducible ventricular tachycardia could not be suppressed with any medical regimen attempted. In 7 of these 12 patients, a regimen consisting of mexiletine either alone or in combination with one or more other agents proved to be the best partially suppressive therapy. Thus, in 20 of 35 patients with electrically inducible ventricular arrhythmias, mexiletine constituted all or part of the final antiarrhythmic regimen.

Rapid ventricular tachycardias were more likely than slower tachycardias to be sensitive to mexiletine (Table II). Inducible tachycardias with rates below 185 beats/min (mean rate 155 ± 20 beats/min, n = 8) in the absence of antiarrhythmic drugs were not fully suppressed by mexiletine. In contrast, 52 percent (11 of 21) of the more rapid tachycardias (mean rate 230 ± 23 beats/min) were fully suppressed by mexiletine. In an additional 4 (19 percent) of 21 patients with rapid ventricular tachycardia, mexiletine, although not fully suppressive, provided the best partially suppressive therapy.

Patients with noninducible tachycardia: Mexiletine resulted in full control of spontaneously occurring arrhythmias in five of six patients with refractory noninducible ventricular tachycardia. However, in one patient, control could be maintained for only 4 days before an adverse reaction (see later) necessitated discontinuation of therapy.

Adverse reactions: Within 48 hours after the start of mexiletine therapy, episodes of spontaneous ventricular tachycardia occurred in four patients. Despite the absence of a clear causal relation, administration of mexiletine was discontinued in these patients and alternate modes of therapy were sought. Three patients exhibited severe neurologic side effects that required discontinuation of mexiletine within the first 5 days of treatment. These reactions were dysphagia and ataxia in one patient, and disabling tremor in two patients. About 50 percent of the patients treated reported minor adverse effects. Tremor at rest, epigastric distress, nausea and lightheadedness were the most common complaints with a peak incidence during the 2 hours after the first morning dose. These gastrointestinal and neurological side effects were usually eliminated by administering mexiletine with food. No evidence of deterioration in cardiac function due to mexiletine was observed in any patient.

Chronic mexiletine therapy: Twenty-four patients were maintained on chronic oral therapy with mexiletine (Table III). Fifteen of the 17 patients whose arrhythmias were suppressed during the acute phase of treatment remain free of recurrent arrhythmias at a mean follow-up period of 12.6 ± 6 months. One patient died after 12 months of mexiletine therapy as a result of refractory progressive heart failure. The other death occurred suddenly 15 months after hospital discharge and was presumably due to a ventricular arrhythmia. Two deaths have occurred among the seven patients in whom mexiletine therapy only partially suppressed the ability to electrically induce ventricular tachycardia. One other patient (Case 7) continues to experience tachycardias that he reliably terminates with a self-activated radiofrequency pacemaker.[14] The other four patients in this group remain free of arrhythmia at a mean follow-up time of 6.7 ± 4 months. No patient in this series experienced the onset of a major mexiletine-induced adverse effect during chronic therapy.

TABLE III

Chronic Mexiletine Therapy

Initial Response	Alive and Well (n)	Repeat VT/VF (SCD) (n)	Other Death	Follow-Up* (mo)
Complete suppression (17 patients)	15	1	1	12.6 ± 6
Partial suppression (7 patients)	5	2	—	6.7 ± 4

* Mean duration ± standard deviation.
SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

Discussion

Antiarrhythmic effectiveness of mexiletine: In this study mexiletine proved to be useful in approximately 50 percent of patients with life-threatening ventricular arrhythmias that were refractory to treatment with all conventionally available antiarrhythmic agents. Previous investigators have reported satisfactory control of ventricular arrhythmias in from 40 to 90 percent of mexiletine-treated patients.[1–7] These authors used a reduction in the frequency and grade of spontaneous ventricular arrhythmia as the end point by which antiarrhythmic efficacy was assessed. However, most of these studies do not describe whether their patients had been responsive to other antiarrhythmic agents and, moreover, often only the acute suppression of ventricular arrhythmia is described without long-term follow-up. In our series, mexiletine was acutely effective in suppressing ventricular tachycardia in 42 percent (17 of 41) of patients. Furthermore, the results of acute drug testing with mexiletine were predictive of the absence of recurrent ventricular arrhythmias in a large majority (94 percent) of the cases at a mean follow-up time of 1 year. Because all the patients in our series were refractory to conventional antiarrhythmic drugs, the response to mexiletine of a less highly selected population of patients with recurrent ventricular arrhythmias might be considerably greater.

Mexiletine seemed to be more effective in suppressing rapid, rather than slow, inducible arrhythmias. When the results of therapy are analyzed with respect to the patients' presenting clinical arrhythmia, we found that 11 of the 15 patients with ventricular fibrillation, 14 of whom manifested rapid ventricular tachycardia at electrophysiologic study, were effectively treated with mexiletine whereas only 5 of 20 patients with recurrent ventricular tachycardia whose arrhythmias were electrically inducible were discharged on the drug. The mechanism responsible for this apparent rate-dependent sensitivity is unknown.

Adverse effects: Adverse effects appearing late after hospital discharge were not observed in the 24 patients maintained on long-term mexiletine therapy. This feature is an important advantage when long-term therapy is based on the results of intensive investigations during a brief in-hospital stay. During long-term therapy with procainamide, the late appearance of a lupus-like syndrome may frequently require discontinuation of a previously effective program. More rarely, patients initially responsive to quinidine may manifest late adverse effects or sensitivity that may similarly require a change in therapy. Aggravation of heart failure frequently complicates disopyramide therapy in patients with underlying left ventricular dysfunction.[15] In patients with prior life-threatening ventricular arrhythmias, such late complications frequently necessitate rehospitalization for additional antiarrhythmic drug testing. Although several of our patients were unable to tolerate standard doses of mexiletine, the major adverse effects were apparent within the first several days of therapy and all the patients discharged on mexiletine therapy were able to continue taking it throughout the follow-up period. In our experience with mexiletine in more than 80 patients, only 2 have required discontinuation of therapy because of adverse effects that appeared after the 1st week of therapy. When plasma levels become routinely available more precise individual dosage regimens can be designed that may lessen the incidence of dose-related toxicity.

Implications: Mexiletine appears to be a promising new antiarrhythmic agent that is capable of suppressing ventricular arrhythmias resistant to all conventionally available drugs in a significant proportion of patients. Electrically induced tachycardias with short cycle lengths as well as tachycardias not inducible by our techniques seem most likely to respond favorably. Therapy, once established, is well tolerated on a reasonable dosage schedule with minimal adverse effects and with no clinically discernible effect on left ventricular function.

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Electrophysiologic Effects of Ouabain in Patients With Preexcitation and Circus Movement Tachycardia

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Effects of intravenous ouabain were evaluated in 19 patients with an anomalous conduction pathway (14 with manifest and 5 with concealed preexcitation) utilizing intracardiac stimulation and recording. Anterograde conduction through the anomalous pathway was present in all 14 patients with manifest preexcitation at a maximal atrial paced rate of 140 to 250 beats/min (mean ± standard error of the mean 214 ± 7.2) before and at 150 to 240 beats/min (mean 206 ± 7.1) after ouabain (difference not significant [NS]). The anterograde effective refractory period of the anomalous pathway, measured at an equivalent atrial paced rate in 10 patients, was 250 to 450 ms (mean 309 ± 19.7) before and 260 to 450 ms (mean 300 ± 17.2) after ouabain (NS). Retrograde conduction through the anomalous pathway was possible at maximal ventricular paced rates (17 patients) of 160 to 250 beats/min (mean 222 ± 6.6) before and 190 to 250 beats/min (mean 221 ± 4.4) after ouabain (NS). Sustained atrioventricular (A-V) reentrant paroxysmal supraventricular tachycardia was inducible in all 19 patients before and in 17 patients (89 percent) after ouabain (tachycardia could not be induced in two patients because of increased A-V nodal refractoriness). The mean cycle length of tachycardia in the 17 patients was 320 ± 6.7 ms before and 340 ± 8.1 ms after ouabain ($p < 0.01$).

In conclusion, ouabain has no significant effect on either anterograde or retrograde anomalous pathway refractoriness. Although ouabain slightly increases the cycle length of tachycardia, it does not interfere with induction of tachycardia in most patients with preexcitation. Oral cardiac glycosides alone would appear to be of limited value in patients with preexcitation and recurrent supraventricular tachycardia.

Wellens and Durrer[1] reported the electrophysiologic effects of intravenously administered ouabain in six patients with the Wolff-Parkinson-White syndrome. They observed a mean decrease in anomalous pathway refractoriness of 28 ms after ouabain, and concluded that cardiac glycosides shorten anomalous pathway refractoriness. They also noted that ouabain interfered with induction of paroxysmal atrioventricular (A-V) reentrant supraventricular tachycardia in two of four patients with this arrhythmia. The effects of ouabain on retrograde conduction through the anomalous pathway were not specifically studied. In 10 patients with preexcitation who had atrial fibrillation induced by rapid atrial stimulation before and after administration of ouabain, Sellers et al.[2] found that ventricular rates were unchanged in one patient, decreased in six patients and increased in three. They related the increase in ventricular rate during atrial fibrillation (due to digitalis) to provocation of ventricular fibrillation.

In this study, we examined the effects of ouabain on electrophysiologic properties in 19 patients with either manifest or concealed preexcitation

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and recurrent paroxysmal supraventricular tachycardia. We specifically evaluated the effects of this agent on anterograde and retrograde anomalous pathway properties, as well as on the ability to induce (from both atrium and ventricle) and sustain circus movement A-V reentrant tachycardias. Our results differ in some important respects from those previously reported.

Methods

Patient selection: The study group consisted of 19 patients, 15 male and 4 female, with anomalous A-V pathways undergoing electrophysiologic studies for documented recurrent paroxysmal supraventricular arrhythmia (17 with paroxysmal supraventricular tachycardia and 2 with paroxysmal atrial fibrillation). The subjects ages ranged from 12 to 64 years (mean ± standard error of the mean 43 ± 3.7).

Fourteen patients had manifest typical preexcitation (left-sided in nine and right-sided in five). Five patients had no anterograde preexcitation, but did have concealed left-sided anomalous A-V connections conducting in retrograde fashion.[3–5]

Electrophysiologic studies: The patients were studied in the postabsorptive nonsedated state after giving informed written consent. Antiarrhythmic therapy was discontinued at least 72 hours before the time of study. His bundle electrograms were recorded using previously described catheter techniques.[6] A hexapolar catheter, introduced through a right antecubital vein, was positioned at the right ventricular apex. The distal two electrodes of this catheter were utilized for right ventricular pacing; the proximal four electrodes were positioned against the right lateral atrial wall and were used for high and mid right atrial recording and stimulation. A third quadripolar electrode catheter, introduced through a left antecubital vein, was used for recording and stimulation from the coronary sinus. Recordings were obtained on a multichannel oscilloscopic photographic recorder (DR-20, Electronics for Medicine) at paper speeds of 100 and 200 mm/s. Simultaneous electrocardiographic leads I, II, III and V_1 were also recorded.

Incremental atrial pacing was performed in increments of 10 beats/min until one or more of the following was achieved: (1) a maximal atrial paced rate of 200 to 250 beats/min, (2) induction of paroxysmal supraventricular tachycardia, or (3) A-V nodal Wenckebach periodicity, or both (2) and (3). The minimal atrial paced rates at which anterograde block occurred in the anomalous pathway were noted. Anterograde refractory periods of the normal and anomalous pathways were determined during atrial paced drive using the extrastimulus technique as previously described.[7]

Anomalous pathway retrograde properties were studied utilizing response to incremental ventricular pacing and the ventricular extrastimulus technique.[8] Retrograde anomalous pathway conduction during supraventricular tachycardia was proved in all cases (both left- and right-sided anomalous connections) by one or more of the following criteria: (1) abnormal retrograde atrial activation sequence[8–10]; (2) ability to capture the atria during supraventricular tachycardia with critically timed ventricular extrastimuli delivered when the His bundle was refractory[11]; and (3) increase in ventriculoatrial (V-A) conduction time during supraventricular tachycardia with development of bundle branch block ipsilateral to the anomalous pathway.[12]

The presence of retrograde anomalous pathway conduction during incremental ventricular pacing was suggested by demonstration of one or more of the following criteria: (1) abnormal retrograde atrial activation sequence (early activation of atrium contiguous to the mid or lateral coronary sinus) detected in patients with a left-sided anomalous pathway (nine patients)[13]; (2) induction of supraventricular tachycardia with incremental ventricular pacing not related to a critical V-A interval, suggesting induction through block in the normal pathway (seven patients with a left-sided and two patients with a right-sided anomalous pathway)[14]; (3) fixed V-A conduction time during incremental ventricular pacing (17 patients)[9]; and (4) retrograde atrial activation sequence during incremental pacing identical to that observed during induced paroxysmal supraventricular tachycardia or A-V reentrant atrial echoes (17 patients).

The ventricles were paced at rates slightly above sinus rate and then in increments of 10 beats/min until one of the following was achieved: (1) a maximal paced rate of 200 to 250/min (depending on clinical status of the patient); (2) induction of paroxysmal supraventricular tachycardia; and (3) development of V-A block. The minimal ventricular paced rates at which retrograde block occurred in the anomalous pathway as suggested by either V-A block during anomalous pathway conduction or sudden prolongation of V-A conduction with concomitant change in atrial activation sequence were noted.

Ouabain administration: During anterograde and retrograde studies, the ability to induce and sustain paroxysmal supraventricular tachycardia as well as the cycle length of induced tachycardia were noted. All of these measurements were completed before administration of ouabain. After control measurements were made, 0.01 mg/kg of ouabain was administered intravenously.[1,15,16] Electrophysiologic studies were initiated 30 minutes later. No arrhythmias typically due to digitalis intoxication were noted. Refractory periods were measured at identical driven cycle lengths before and after ouabain (cycle length range 400 to 600 ms; mean 502 ± 18 ms).

Definitions: *The anterograde effective refractory period of the anomalous pathway* was defined as the longest atrial coupling interval at which block was achieved in the anomalous pathway (disappearance of delta wave). Anomalous pathway refractory periods were measured from the same site before and after administration of the drug. This site was close to the anomalous pathway location in most of the patients.[17]

The retrograde effective refractory period of the anomalous pathway was defined as the longest ventricular coupling interval ($V_1 - V_2$) at which V_2 failed to conduct to the atria through the anomalous pathway as suggested by either V-A block or a sudden increase and normalization of retrograde atrial activation sequence.[10] Ventricular pacing was performed from the right ventricular apex.

Paroxysmal supraventricular tachycardia was defined (for the purpose of this study) as A-V reentrant tachycardia utilizing the normal pathway for anterograde conduction and the anomalous pathway for retrograde conduction. No patient had sustained tachycardia utilizing the anomalous pathway in anterograde and the normal pathway in retrograde fashion. The tachycardia was defined as sustained if it lasted 30 seconds or more, necessitating termination with atrial or ventricular stimulation.

Results

Anomalous pathway anterograde and retrograde properties (Table I): Ability for intact (1:1) anomalous pathway anterograde conduction (a measurement related to anomalous pathway refractoriness) was demonstrated in all 14 patients with manifest preexcitation

TABLE I

Selected Electrophysiologic Findings in 19 Patients

Case	Age (yr) & Sex	Type of pre-excitation	Max AR With preexcitation (beats/min)		Anterograde KERP (ms)		Max VR With 1:1 V-A Conduction (beats/min)		Ability to Induce Sustained PSVT		PSVT Cycle Length (ms)	
			C	O	C	O	C	O	C	O	C	O
1	47M	B	210	210	275	275	210	200	Yes	Yes	380	387
2	64M	A	230	230	270	290	—	—	Yes	Yes	280	290
3	30M	A	250	240	—	—	230	230	Yes	Yes	289	299
4	50M	A	210	200	—	—	230	230	Yes	No	285	—
5	24M	B	240	220	250	260	220	220	Yes	Yes	280	310
6	38M	A	210	220	—	—	200	190	Yes	Yes	320	335
7	43M	B	200	200	365	300	190	200	Yes	Yes	305	314
8	38F	B	140	150	450	450	220	220	Yes	Yes	316	328
9	50M	A	200	200	350	310	210	210	Yes	Yes	300	300
10	61M	A	200	200	300	290	—	—	Yes	Yes	300	330
11	55F	B	220	155	—	—	250	250	Yes	Yes	340	400
12	59F	A	230	220	250	280	260	240	Yes	Yes	345	358
13	22M	A	240	230	290	270	270	250	Yes	Yes	340	360
14	31M	A	220	220	290	280	250	240	Yes	Yes	330	320
15	61M	CKB	—	—	—	—	210	210	Yes	Yes	350	350
16	24F	CKB	—	—	—	—	240	240	Yes	No	360	—
17	12M	CKB	—	—	—	—	200	210	Yes	Yes	350	380
18	41M	CKB	—	—	—	—	220	220	Yes	Yes	320	340
19	42F	CKB	—	—	—	—	160	210	Yes	Yes	305	380

AR = atrial rate; C = control period (before ouabain); CKB = concealed Kent bundle; KERP = effective refractory period of Kent bundle (anomalous pathway); Max AR = maximal atrial paced rate; Max VR = maximal ventricular paced rate; O = after ouabain; PSVT = paroxysmal supraventricular tachycardia; V-A = ventriculoatrial; VR = ventricular rate.

at maximal atrial paced rates of 140 to 250 beats/min (mean 214 ± 7.2) before and at 150 to 240 beats/min (mean 206 ± 7.1) after ouabain (NS). The anterograde effective refractory period of the anomalous pathway could be measured at identical cycle lengths in 10 of the 14 patients with manifest preexcitation before and after ouabain. In four patients, atrial refractoriness limited the measurement of the anomalous pathway anterograde refractory period. The anomalous pathway effective refractory period ranged from 250 to 450 ms (mean 309 ± 19.7) during the control period and from 260 to 450 ms (mean 300 ± 17.2) after administration of ouabain (NS) (Fig. 1).

Seventeen patients had intact retrograde anomalous pathway conduction at the maximal tested paced rates of 160 to 260 beats/min both before and after ouabain. The maximal paced heart rate for intact retrograde anomalous pathway conduction in these patients ranged from 160 to 260 beats/min (mean 222 ± 6.6) before and 190 to 250 beats/min (mean 221 ± 4.4) after administration of ouabain (NS). In two patients, retrograde anomalous pathway conduction was not tested with incremental ventricular pacing.

The retrograde effective refractory period of the anomalous pathway could be measured in 11 patients before and after administration of ouabain. The refractory periods in these patients ranged from 225 to 290 ms (mean 260 ± 7.4) before and from 225 to 310 ms (mean 261 ± 9.5) after ouabain (NS). Ventricular refractoriness precluded measurement of the retrograde anomalous pathway refractory period in the remaining eight patients. Ventricular refractory periods, measured in 16 patients, ranged from 160 to 270 ms (mean 231 ± 8.8 ms) before and from 160 to 270 ms (mean 228 ± 8.9) after administration of ouabain (NS).

Effect on paroxysmal supraventricular tachycardia (Table I): Sustained tachycardia could be induced in all 19 patients (100 percent) before administration of ouabain with use of one or more of the following techniques: (1) sudden cessation of rapid atrial

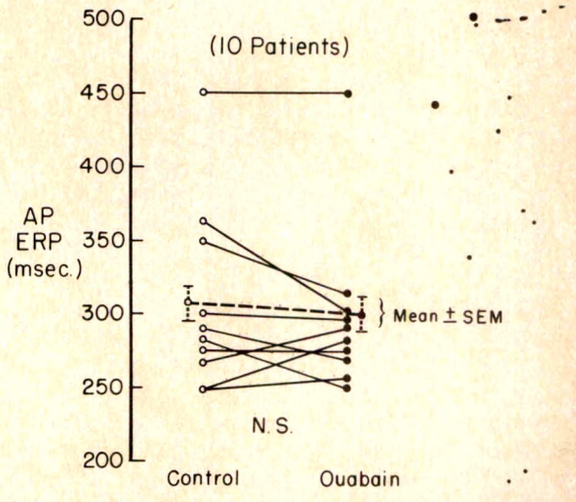

FIGURE 1. The effects of ouabain on anomalous pathway (AP) anterograde effective refractory periods (ERP) in 10 patients. Control values are shown on the **left,** post-ouabain values on the **right.** Mean values ± standard error of the mean (SEM). N.S. = difference not significant.

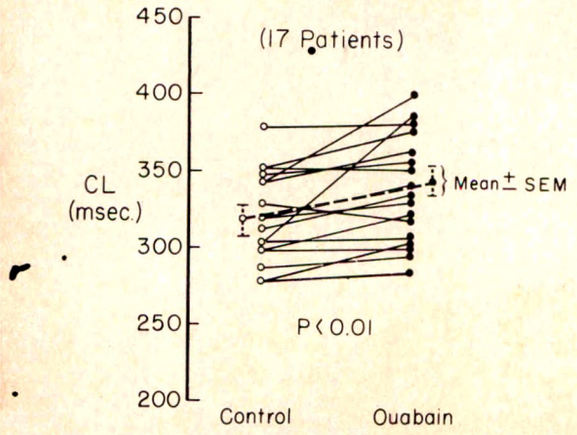

FIGURE 2. Effect of ouabain on the cycle length of induced paroxysmal supraventricular tachycardia before and after ouabain administration in 17 patients. CL = cycle length; P = probability; SEM = standard error of the mean.

pacing (16 patients); (2) atrial extrastimulus technique (9 patients); (3) cessation of rapid ventricular pacing (9 patients) and ventricular extrastimulus technique (6 patients). In all patients, induced paroxysmal supraventricular tachycardia was characterized by anterograde normal pathway conduction and retrograde anomalous pathway conduction.

In 17 (89 percent) of 19 patients, induction of sustained tachycardia was possible both before and after ouabain administration using identical stimulatory techniques. Tachycardia cycle lengths in these 17 patients ranged from 280 to 380 ms (mean 320 ± 6.7) before and from 290 to 400 ms (mean 340 ± 8.1) after ouabain ($p < 0.01$). This change in tachycardia cycle length was equivalent to a decrease in the rate of paroxysmal supraventricular tachycardia of 14 beats/min (heart rate 190 beats/min before and 176 beats/min after ouabain). The longer cycle lengths after ouabain reflected an increase in A-V nodal conduction (A-H interval) during paroxysmal supraventricular tachycardia, without change in H-A intervals (Fig. 2). In 2 (10 percent) of the 19 patients, the ability to induce paroxysmal supraventricular tachycardia was lost after ouabain administration. This loss reflected an increase in A-V nodal refractoriness that prevented repetitive sequential anterograde normal pathway conduction.

Discussion

Mechanism of paroxysmal supraventricular tachycardia and atrial fibrillation in Wolff-Parkinson-White syndrome: Current evidence suggests that patients with the Wolff-Parkinson-White syndrome have an extranodal anomalous pathway that bypasses the normal A-V nodal conduction system.[9–13,17–19] These patients are prone to A-V reentrant paroxysmal supraventricular tachycardia. Such tachycardia in patients with the Wolff-Parkinson-White syndrome is most commonly characterized by narrow QRS complexes, and reflects a circus movement with anterograde conduction in the normal A-V nodal pathway and retrograde conduction in an anomalous extranodal pathway. Induction of paroxysmal supraventricular tachycardia can be achieved either from the atrium, with atrial impulses that block in the anomalous pathway and conduct in anterograde fashion through the normal pathway, or from the ventricle, with ventricular impulses that block in the normal pathway and conduct in retrograde manner through the anomalous pathway.[20]

Patients with preexcitation are also susceptible to atrial fibrillation.[21–25] The mechanism of atrial fibrillation in patients with the Wolff-Parkinson-White syndrome is not thoroughly understood. In some patients, A-V reentrant paroxysmal supraventricular tachycardia and atrial fibrillation appear to be related, as evidenced by the observation of paroxysmal supraventricular tachycardia spontaneously degenerating into atrial fibrillation.[22–24] In other patients, associated organic heart disease, sinoatrial dysfunction or other as yet unmeasured atrial properties may play a role in the occurrence of paroxysmal atrial fibrillation. In patients with preexcitation and paroxysmal atrial fibrillation, the ventricular rate is determined by anterograde anomalous pathway refractoriness.[21–25]

Effects of digitalis in preexcitation syndrome: The use of digitalis in patients with preexcitation could have potentially beneficial as well as deleterious effects on arrhythmias complicating preexcitation.[1,2] If digitalis increased A-V nodal refractoriness to a critical degree, it might interfere with ability to sustain A-V reentrant tachycardia, and result in cure of recurrent paroxysmal supraventricular tachycardia. In patients with atrial fibrillation complicating preexcitation, if digitalis decreased anterograde anomalous pathway refractoriness, it would result in increased ventricular rates during this arrhythmia.[21] Independent of its effect on anomalous pathway refractoriness, digitalis (particularly at toxic levels) could make the ventricles more prone to ventricular fibrillation.

Electrophysiologic techniques have provided some insight into the potential values and hazards of digitalis in patients with the Wolff-Parkinson-White syndrome.[1,2] Wellens and Durrer[1] studied the effects of intravenous ouabain in six patients with preexcitation (type A in four and type B in two), noting that this agent shortened anomalous pathway anterograde refractoriness in all. Anomalous pathway effective refractory period ranged from 230 to 360 ms (mean 305) before and from 210 to 350 ms (mean 277) after ouabain. Statistical analysis of these results was not reported. The decrease in anomalous pathway refractoriness demonstrated by Wellens and Durrer[1] suggested that digitalis would probably increase ventricular rates in patients with atrial fibrillation complicating preexcitation. Sellers et al.[2] studied this question more directly, by examining the effect of intravenous digoxin on atrial fibrillation induced by atrial stimulation in 10 patients with preexcitation. In contrast to what might have been expected, they noted a mean increase in ventricular cycle length of 69 ms during atrial fibrillation (from 379 ms

before to 448 ms after digoxin). Specifically, they noted slowing of ventricular rate in six patients, no change in ventricular rate in one patient, and increase in ventricular rate in three patients. They suggested that the decrease of ventricular cycle length seen in some patients (increase in ventricular rates) might relate to provocation of ventricular fibrillation.

The question arises whether our results can be reconciled with those of the preceding reports. In summary, we demonstrated no significant effect of ouabain on either anterograde or retrograde anomalous pathway refractoriness, utilizing the atrial extrastimulus technique, atrial incremental pacing, ventricular extrastimulus technique and incremental ventricular pacing. We noted a loss of ability to induce sustained paroxysmal supraventricular tachycardia in only 2 (10 percent) of 19 patients after ouabain. We did note slight (but significant) slowing of cycle length of induced paroxysmal tachycardia in the remaining 17 patients after ouabain. We did not attempt induction of atrial fibrillation before and after ouabain.

Our own statistical analysis of the previously reported 16 cases,[1,2] utilizing the unpaired *t* test, revealed that ouabain had no significant effect on anomalous pathway refractoriness (Wellens and Durrer[1]) and no significant effect on ventricular rates or shortest observed R-R interval during atrial fibrillation after digoxin (Sellers et al.[2]). Their results would thus seem to be entirely consistent with our demonstration of insignificant effect of ouabain on anterograde anomalous pathway refractoriness. The previously observed changes in some patients of either anomalous pathway refractory periods or ventricular rates during atrial fibrillation following digitalis may in fact be biologic variability of the measured variables, as opposed to a true pharmacologic effect of cardiac glycosides on anomalous pathway properties.

Our observation of lack of effect of ouabain on retrograde anomalous pathway refractoriness is certainly consistent with the lack of effect on anterograde refractoriness. This particular variable of anomalous pathway function has not been systematically studied previously. The ability for retrograde anomalous pathway conduction would relate to ability for sustained circus movement tachycardias in patients with preexcitation. If ouabain were to interfere with induction of paroxysmal tachycardia in preexcitation, it would have to be by affecting the A-V node. Ouabain is known to increase A-V nodal refractoriness.[26] In our study, this increase in A-V nodal refractoriness after ouabain was insufficient to prevent induction of sustained A-V reentrant paroxysmal tachycardia in most of our patients. However, an increase in A-V nodal conduction delay due to ouabain, as manifested by an increase in A-H interval during paroxysmal supraventricular tachycardia, did increase the cycle length of induced tachycardia. Why Wellens and Durrer[1] found ouabain effective in preventing induction of paroxysmal tachycardia in 50 percent of their cases (2 of 4), whereas we found a similar effect in only 10 percent (2 of 19) of patients, may relate to methodology. Wellens and Durrer[1] utilized only atrial extrastimulus induction of tachycardia, whereas we utilized tachycardia induction from either atrium or ventricle. Our approach would seem more reasonable, since there are no data suggesting that only one mode of stimulation is the appropriate one for quantifying drug effects on ability to induce sustained circus movement tachycardias.

Clinical implications: Acute intravenous administration of ouabain in patients with preexcitation had no significant effect on anomalous pathway anterograde or retrograde refractoriness. Ouabain prevented induction of circus movement paroxysmal supraventricular tachycardia in only a limited number of cases. However, it significantly increased the cycle length of induced tachycardia by depressing A-V nodal conduction.

Recent reports utilizing long-term electrophysiologic studies in patients with recurrent paroxysmal tachycardia suggest that response to acute intravenous drug administration predicts future response to oral administration of the same drug.[27] The results of our study with intravenous ouabain suggest that in patients with preexcitation (both manifest and concealed), oral glycosides alone would be of limited value in preventing attacks of paroxysmal supraventricular tachycardia. The increase in cycle length of tachycardia produced by this agent would appear to be of limited clinical value.

In patients with paroxysmal atrial fibrillation complicating preexcitation with a short anomalous pathway refractory period, digitalis is generally contraindicated. The lack of significant effect of this agent on anomalous pathway refractoriness, coupled with possible increase in ventricular vulnerability to ventricular fibrillation (particularly if digitalis were used in large amounts), suggests that this agent would be dangerous. There are no data concerning the potential risk of cardiac glycosides in patients with preexcitation who have not had paroxysmal atrial fibrillation.

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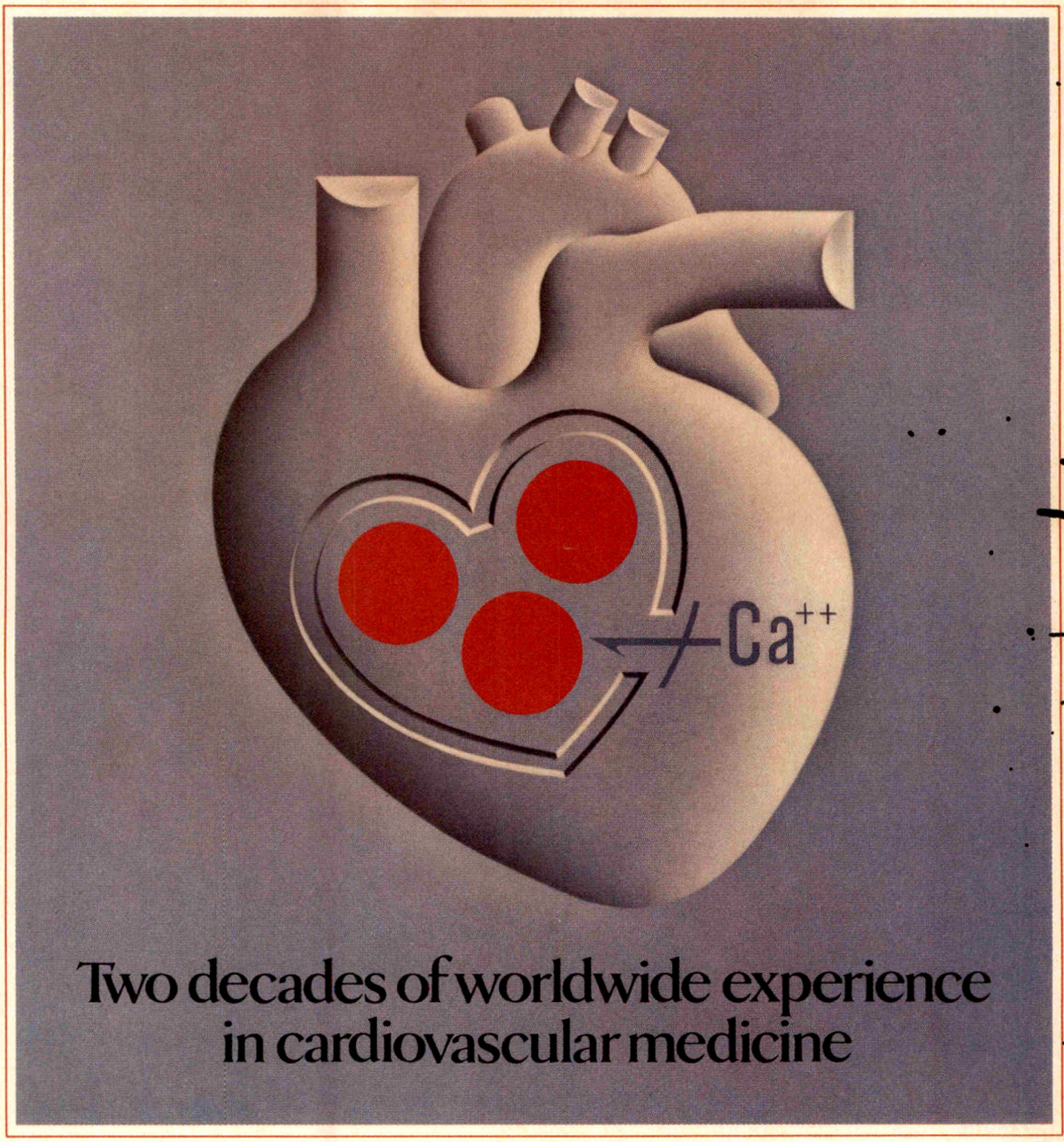

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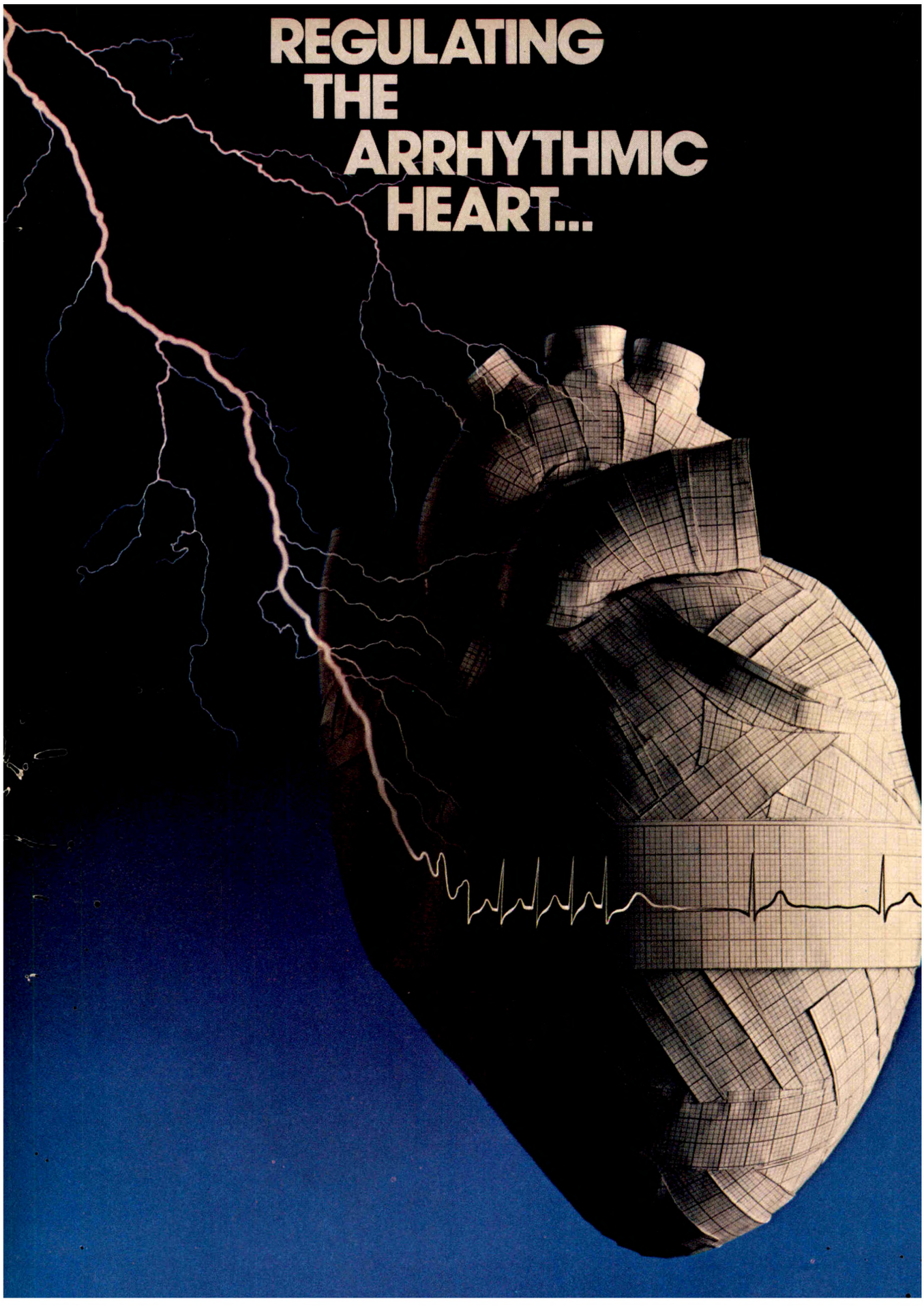
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ALONE Excessive exertions. Emotional upheavals. Anxieties. Stress. Catecholamines rise—atrial pacemakers overrespond. And the ECG reads PAT. Or persistent sinus tachycardia. Or persistent atrial extrasystoles. Consider INDERAL (propranolol HCl) alone. When conventional measures fail, a low 10 to 30 mg dose, given t.i.d. or q.i.d., will block cardiac beta-receptors from excessive catecholamine stimulation. Suppress ectopic pacemakers. And permit resumption of normal sinus rhythm. Even when normal sinus rhythm has not been restored, INDERAL slows conduction in the AV node and prolongs its refractory time. Slowed AV conduction will often block reentry circuits, to help restore sinus rhythm.

WITH The ECG reads atrial flutter. Or atrial fibrillation. You have digitalized your patient, but the arrhythmia is not yet controlled. Consider adding INDERAL (propranolol HCl). Combined with digitalis, it obviates increasing digitalis dosage to toxic levels—while slowing the ventricular rate sufficiently to achieve control. INDERAL also complements the action of other agents. Combined with quinidine, it allows lower doses of quinidine—reducing the need for toxic levels. And often, with INDERAL added, atrial arrhythmias respond when no single agent works alone.

INSTEAD The arrhythmia is induced by an antiarrhythmic drug such as digitalis or quinidine. Persists after discontinuance of the drug and correction of electrolyte imbalance. Consider INDERAL instead. Often the drug of choice, except in the presence of serious congestive heart failure. Often, too, INDERAL (propranolol HCl) abolishes supraventricular arrhythmias when either digitalis or quinidine has failed.

With proper patient selection—in the absence of contraindications such as bradycardia, greater than first degree heart block, asthma, and congestive heart failure unless failure is secondary to tachyarrhythmias treatable with INDERAL—serious cardiovascular and respiratory side effects are seldom encountered.* Rely on it: INDERAL. Alone. With. Or Instead.

*Please turn the page for brief summary of prescribing information on contraindications, adverse reactions, and warnings, including avoidance of abrupt withdrawal.

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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)
Inderal® BRAND OF propranolol hydrochloride **A beta-adrenergic blocking agent**

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS: INDERAL is a beta-adrenergic receptor blocking drug, possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available beta receptor sites. When access to beta receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

Propranolol is almost completely absorbed from the gastrointestinal tract, but a portion is immediately bound by the liver. Peak effect occurs in one to one and one-half hours. The biologic half-life is approximately two to three hours. Propranolol is not significantly dialyzable. There is no simple correlation between dose or plasma level and therapeutic effect, and the dose-sensitivity range as observed in clinical practice is wide. The principal reason for this is that sympathetic tone varies widely between individuals. Since there is no reliable test to estimate sympathetic tone or to determine whether total beta blockade has been achieved, proper dosage requires titration.

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol exerts its antiarrhythmic effects in concentrations associated with beta-adrenergic blockade and this appears to be its principal antiarrhythmic mechanism of action. The membrane effect also plays a role, particularly, some authorities believe, in digitalis-induced arrhythmias.

Beta-adrenergic blockade is of unique importance in the management of arrhythmias due to increased levels of circulating catecholamines or enhanced sensitivity of the heart to catecholamines (arrhythmias associated with pheochromocytoma, thyrotoxicosis, exercise).

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential and depresses cardiac function.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta-adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATIONS: Cardiac Arrhythmias: *1.) Supraventricular arrhythmias:* a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.) b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient. c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy. May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS.) d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures. e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated.

2.) Ventricular tachycardias: Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. a) Ventricular tachycardias: With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice. In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered. If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly. (See DOSAGE AND ADMINISTRATION.) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.* b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3.) Tachyarrhythmias of digitalis intoxication: If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur. (See OVERDOSAGE OR EXAGGERATED RESPONSE.)

Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION.)

4.) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia. Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines. When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring. (See WARNINGS.)

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of INDERAL in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary.

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery.

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed.

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation.

CONTRAINDICATIONS: INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS: CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (i.e., that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use not been adequately appraised. Special consideration should be given to propranolol's p tial for aggravating congestive heart failure. Propranolol may mask the clinical signs of de ing or continuing hyperthyroidism or complications and give a false impression of improv Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of sympt of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propra slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have beer ported in which, after propranolol, the tachycardia was replaced by a severe bradycardia quiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propra

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for tenance of adequate cardiac function, beta blockade will impair the desired inotropic effe Therefore, INDERAL should be titrated carefully when administered for arrhythmias occur during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytom INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and ph siologic effects are gone according to available evidence. However, in case of emergency gery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be versed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, suc tients may be subject to protracted severe hypotension. Difficulty in restarting and maintai the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCH EMPHYSEMA), INDERAL should be administered with caution since it may block broncho tion produced by endogenous and exogenous catecholamine stimulation of beta recepto

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrene blocking activity, INDERAL may prevent the appearance of premonitory signs and sympto (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to k in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a cipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been es-tablished. Use of any drug in pregnancy or women of childbearing potential requires that t possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. bryotoxic effects have been seen in animal studies at doses about 10 times the maximum r ommended human dose.

PRECAUTIONS: Patients receiving catecholamine depleting drugs such as reserpine sho be closely observed if INDERAL is administered. The added catecholamine blocking actio this drug may then produce an excessive reduction of the resting sympathetic nervous act Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or m bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be o served at regular intervals. The drug should be used with caution in patients with impaired or hepatic function.

ADVERSE REACTIONS: *Cardiovascular:* bradycardia; congestive heart failure; intensific of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynau type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, tude, weakness, fatigue; reversible mental depression progressing to catatonia; visual dis bances; hallucinations; an acute reversible syndrome characterized by disorientation for t and place, short term memory loss, emotional lability, slightly clouded sensorium, and de-creased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, c stipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with achi and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpu

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, s rous membranes and conjunctivae reported for a beta blocker (practolol) have not been c clusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe hea ease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DOSAGE AND ADMINISTRATION: The dosage range for INDERAL is different for eac indication.

ORAL

ARRHYTHMIAS—10-30 mg three or four times daily, before meals and at bedtime.

HYPERTROPHIC SUBAORTIC STENOSIS—20-40 mg three or four times daily, before m and at bedtime.

PHEOCHROMOCYTOMA—*Preoperatively*—60 mg daily in divided doses for three days to surgery, concomitantly with an alpha-adrenergic blocking agent.—*Management of inop ble tumor*—30 mg daily in divided doses.

PEDIATRIC DOSAGE At this time the data on the use of the drug in this age group are to ited to permit adequate directions for use.

INTRAVENOUS Intravenous administration is reserved for life-threatening arrhythmias o those occurring under anesthesia. The usual dose is from 1 to 3 mg administered under ca monitoring, *e.g.* electrocardiographic, central venous pressure. The rate of administration should not exceed 1 mg (1 ml) per minute to diminish the possibility of lowering blood press and causing cardiac standstill. Sufficient time should be allowed for the drug to reach the s action even when a slow circulation is present. If necessary, a second dose may be given a two minutes. Thereafter, additional drug should not be given in less than four hours. Additio INDERAL should not be given when the desired alteration in rate and/or rhythm is achieve

Transference to oral therapy should be made as soon as possible.

The intravenous administration of INDERAL has not been evaluated adequately in the m agement of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE: IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

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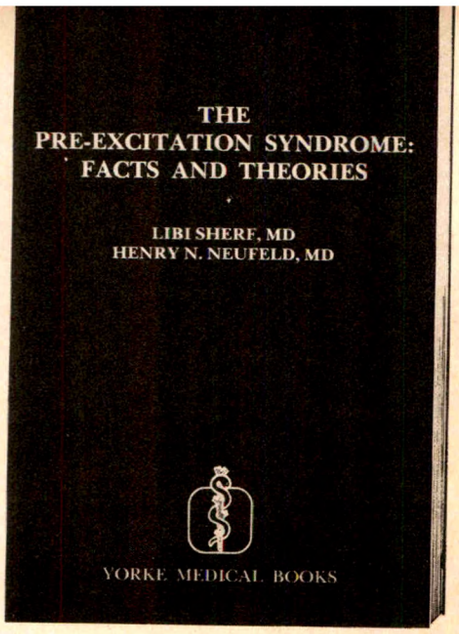

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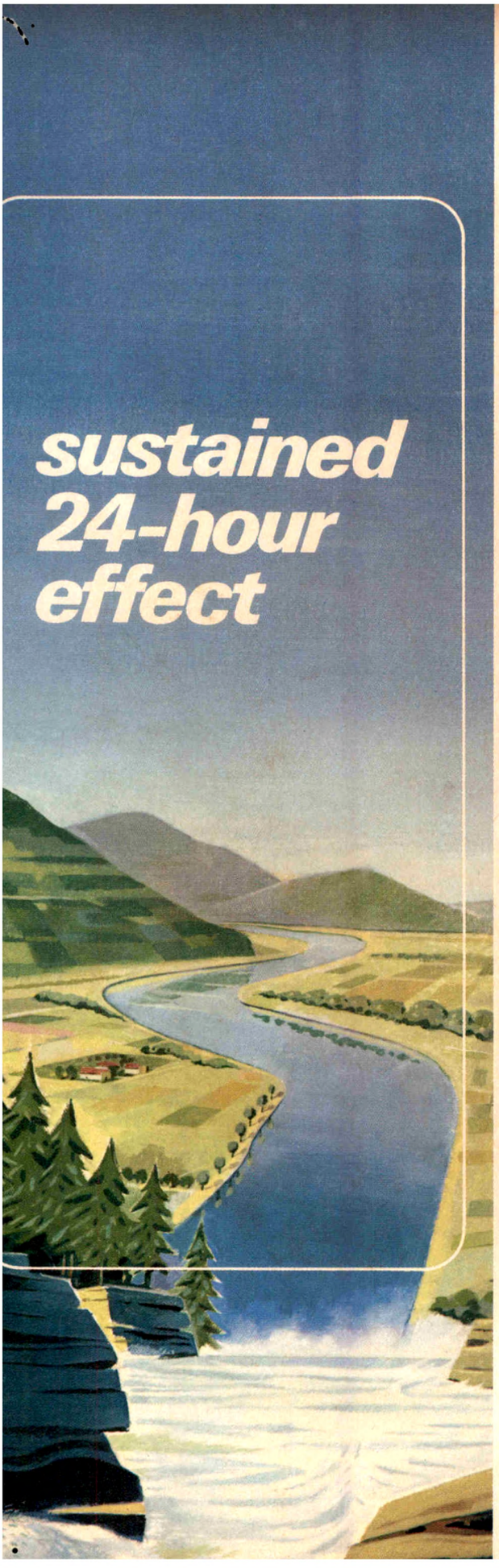

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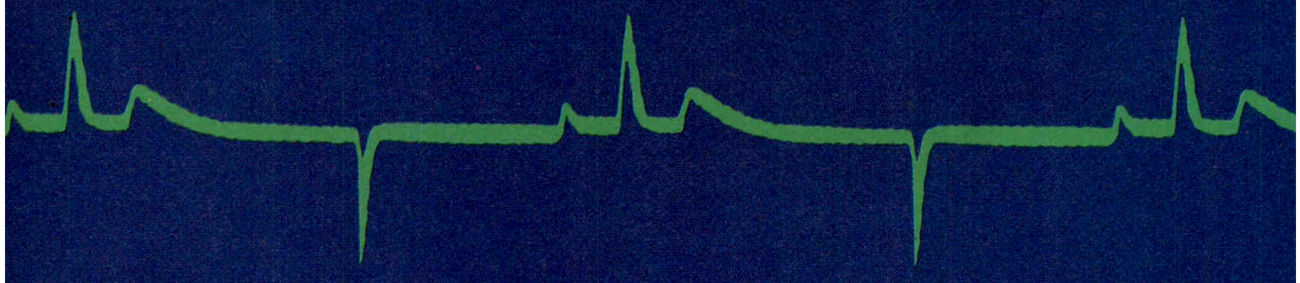

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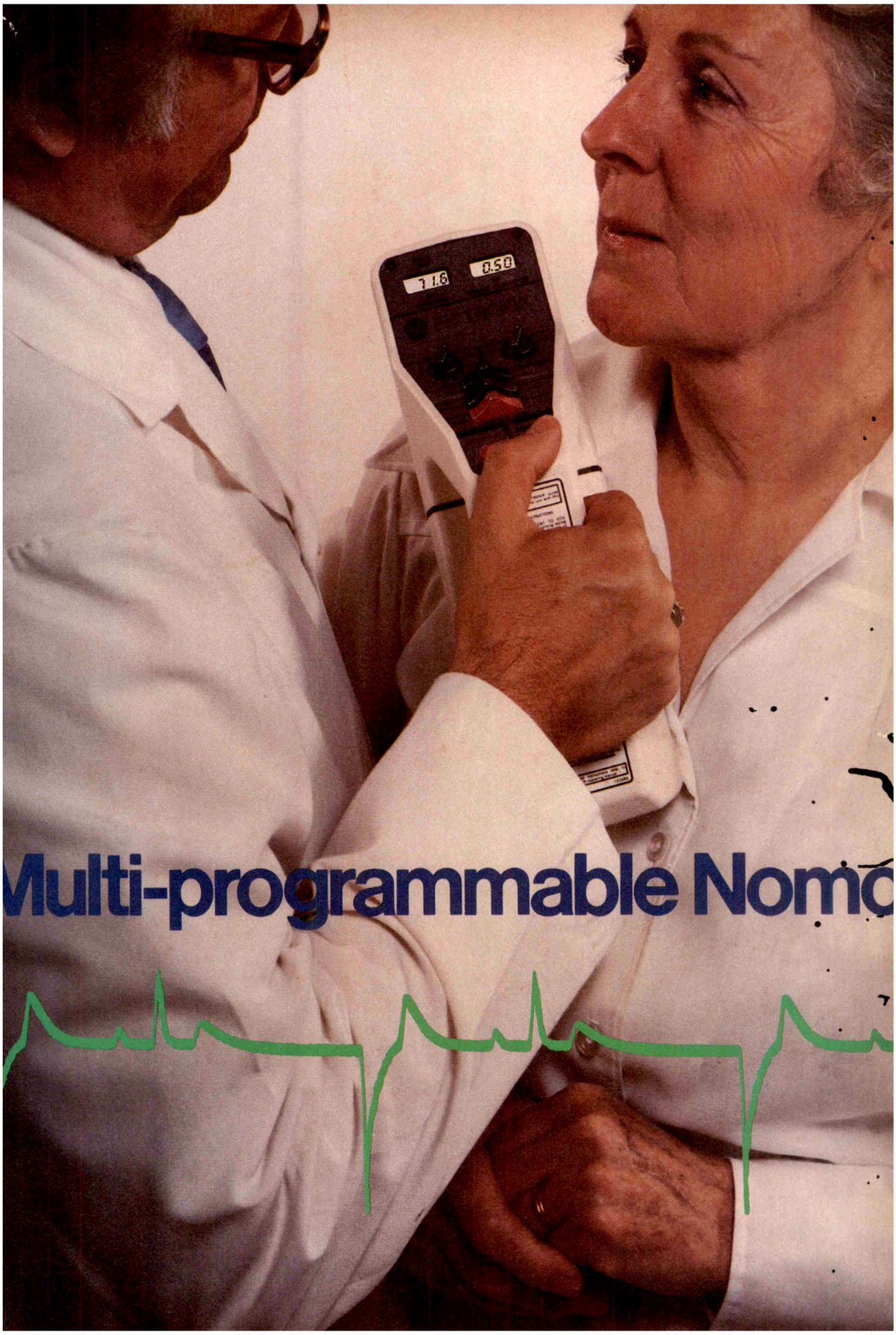
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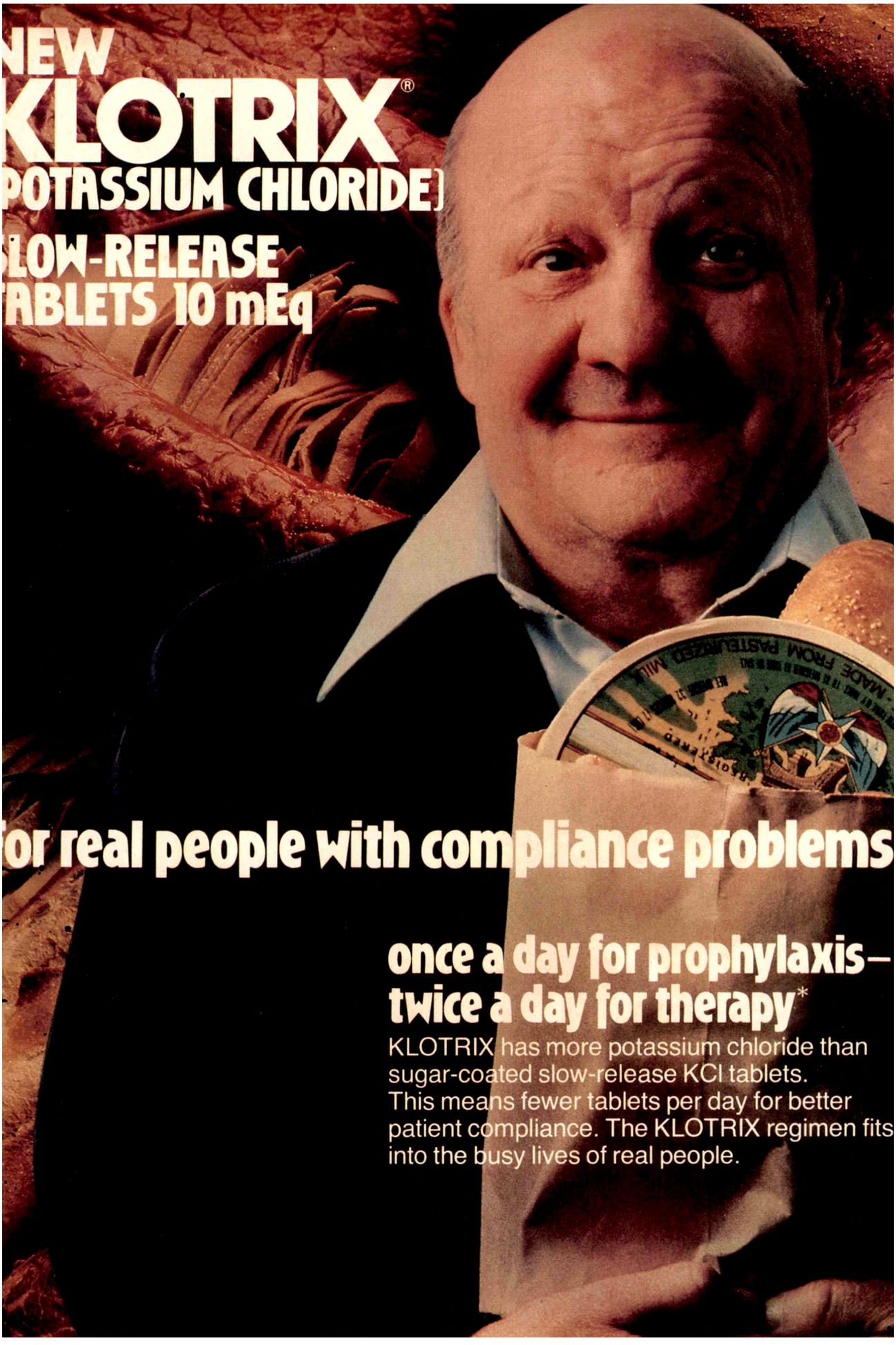
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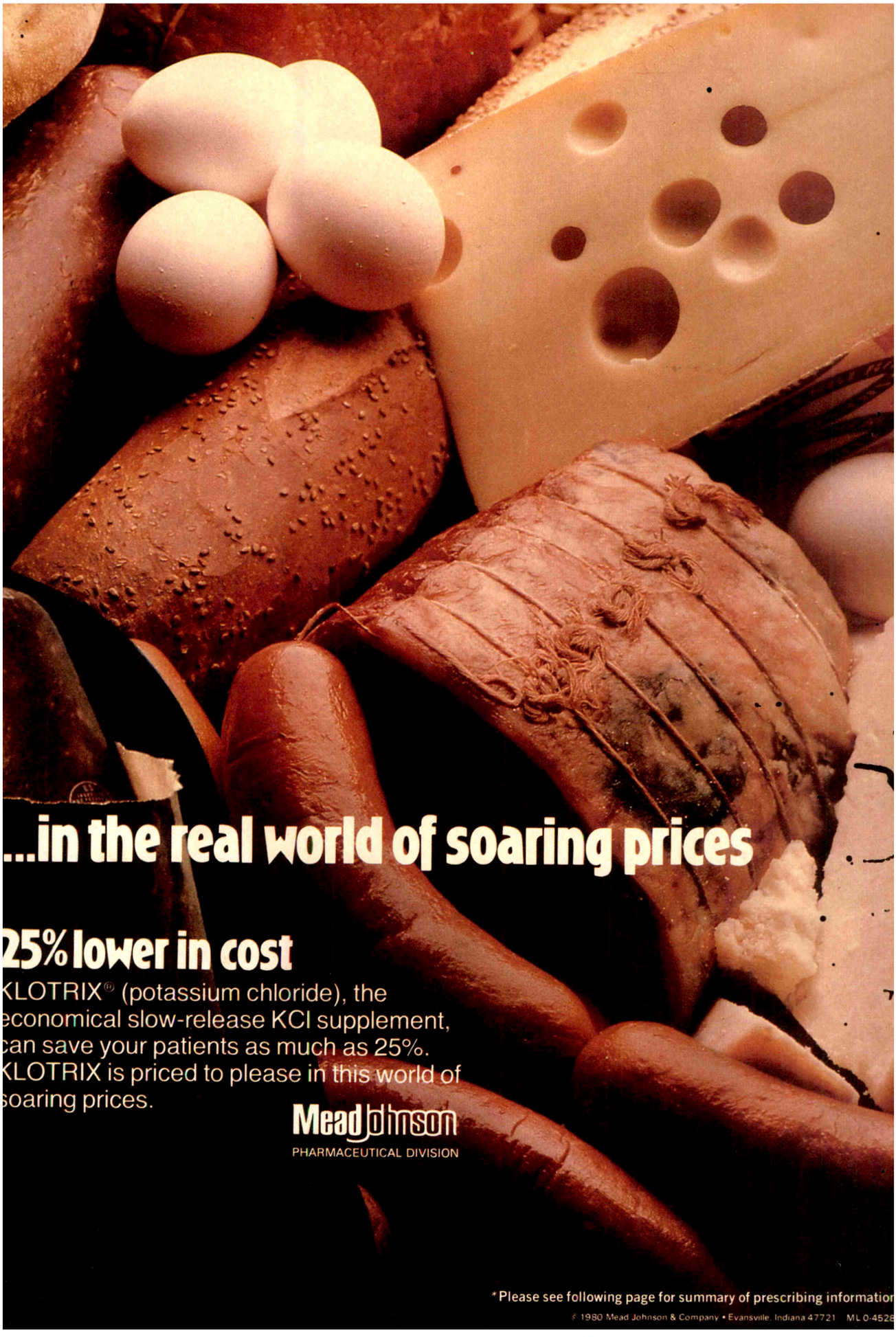
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r prevention of potassium depletion when the dietary intake of potassium is inadequate in the wing conditions: Patients receiving digitalis and diuretics for congestive heart failure; tic cirrhosis with ascites; states of aldosterone excess with normal renal function; sium-losing nephropathy, and certain diarrheal states.
e use of potassium salts in patients receiving diuretics for uncomplicated essential hyper- on is often unnecessary when such patients have a normal dietary pattern. Serum potassium ld be checked periodically, however, and, if hypokalemia occurs, dietary supplementation potassium-containing foods may be adequate to control milder cases. In more severe cases lementation with potassium salts may be indicated.

TRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium entration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of llowing conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the adminis- on of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
matrix potassium chloride preparations have produced esophageal ulceration in certain ac patients with esophageal compression due to enlarged left atrium.
olid dosage forms of potassium supplements are contraindicated in any patient in whom there use for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium lementation should be with a liquid preparation.

NINGS Hyperkalemia: In patients with impaired mechanisms for excreting potassium, nistration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most nonly in patients given potassium intravenously but may also occur when given orally. Poten- fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in nts with chronic renal disease, or any other condition which impairs potassium excretion res particularly careful monitoring of the serum potassium concentration and appropriate ge adjustment.
raction with potassium-sparing diuretics: Hypokalemia should not be treated by the omitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolac- or triamterene), since the simultaneous administration of these agents can produce re hyperkalemia.
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abolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an izing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

CAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a nt with a clinical history suggesting some cause for potassium depletion. In interpreting the m potassium level, the physician should bear in mind that acute alkalosis *per se* can produce kalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can ease the serum potassium concentration into the normal range even in the presence of a total body potassium. Treatment of potassium depletion particularly in presence of cardiac ase, renal disease, or acidosis, requires careful attention to acid-base balance and appropri- monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

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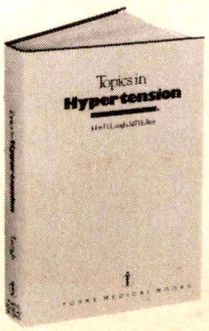

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Observations on Detecting Left Ventricular Thrombus With Two Dimensional Echocardiography: Emphasis on Avoidance of False Positive Diagnoses

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FRANK L. MIKELL, MD
BIM SHARMA, MD
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KIM KARLSON

Minneapolis, Minnesota

Observations made in detecting left ventricular thrombus with two dimensional echocardiography in 25 patients are reviewed. In 20 patients thrombus was documented on angiography, surgery, postmortem examination or serial two dimensional echocardiographic findings; in the remaining five patients two dimensional echocardiographic findings of thrombus were unequivocal. In all 25 patients wall motion abnormalities ranging from hypokinesia to frank dyskinesia were present at the site of the thrombus. Twenty-three patients had an apical thrombus; two had thrombus adjacent to the inferior wall. Clear delineation of the endocardium and thrombus margin was considered essential to the correct diagnosis of thrombus. Both intracavitary motion of the thrombus margin and a layering effect were noted infrequently although they were of benefit in identifying an intracardiac mass as thrombus. In addition, serial evaluations were helpful in establishing the correct diagnosis.

False positive diagnoses can be minimized if one understands certain technical limitations of this method and correctly identifies apical structures that are not thrombi. Axial and lateral resolution problems inherent with this technique can produce intracavitary echoes that may simulate thrombi. In addition, normal or pathologic structures at the apex may also simulate thrombi. These structures include the papillary muscles, muscular trabeculae, chordal structures and tangential information from normal myocardium. Varying the sector orientation or acoustic window, or both, will aid in correctly identifying these structures and distinguishing them from left ventricular thrombi.

Left ventricular thrombus is a common postmortem finding in the settings of acute myocardial infarction,[1–3] congestive cardiomyopathy[3] and left ventricular aneurysm.[1,3,4] However, before the availability of two dimensional echocardiography, the presence of thrombus became clinically apparent only if an embolic event occurred or if detection was made by contrast ventriculography. Embolic events that occur in these clinical conditions can cause significant morbidity and occasional death. Randomized trials of anticoagulation in acute myocardial infarction have not shown a significant decrease in mortality in the groups receiving therapy,[5–7] but a significant reduction in the incidence of systemic embolism has been noted.[6,7] The presumed mechanism for embolic events during acute myocardial infarction is mural thrombus followed by peripheral embolization. Two dimensional echocardiography is a method that can potentially detect left ventricular thrombus before embolization. Thus, this technique may make it possible to institute appropriate therapy in patients after infarction and prevent or decrease the incidence of embolization.

When two dimensional echocardiography is applied to the evaluation of patients at risk for left ventricular thrombus, it is important to establish prospectively guidelines for the accurate diagnosis of such

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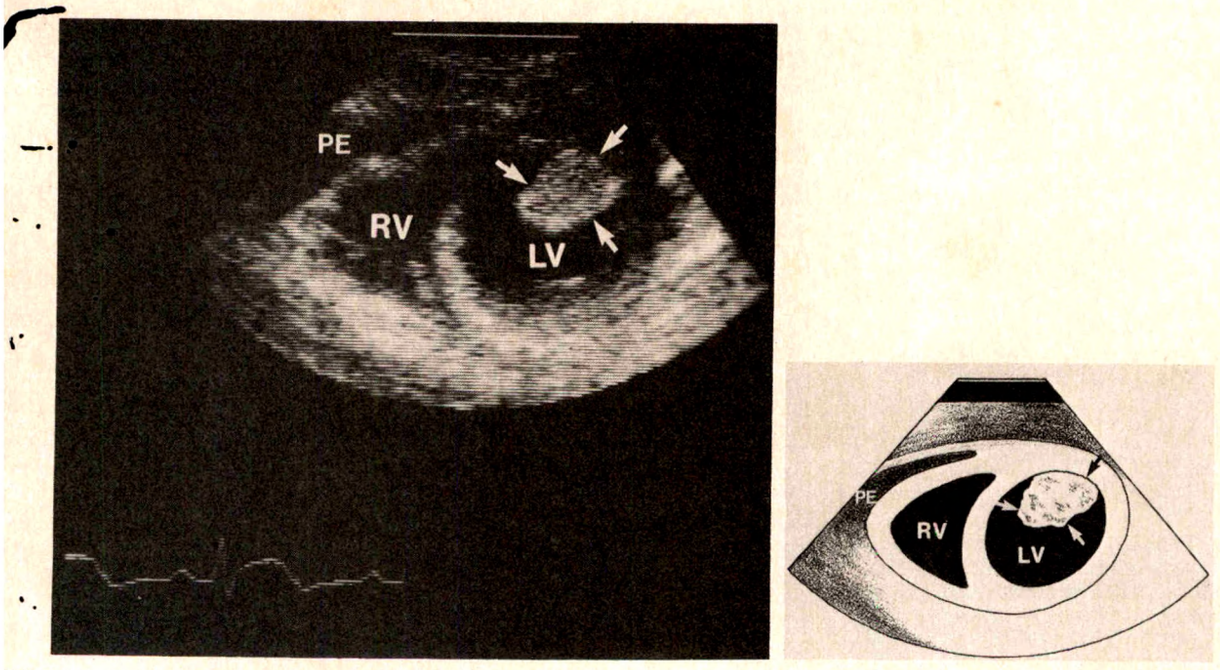
ırombus. From angiographic, surgical and post-ıortem correlative observations, we have found that vo dimensional echocardiography is a sensitive :chnique for detecting such thrombus. An appre-ation of the inherent limitations of two dimensional :hocardiography and knowledge of left ventricular ıatomy are necessary to avoid the misdiagnosis of ırombus. In this review we note our observations in ətecting and characterizing left ventricular ırombus using two dimensional echocardiography 25 patients with particular emphasis on avoidance ' false positive interpretations.

Methods

Study patients: These observations were made from a se-ɛs of 2,657 consecutive two dimensional echocardiographic udies performed at this institution over a 27 month period. ɔrty-one patients with echocardiographic findings consid-ed highly suggestive (n = 25) or characteristic (n = 16) of left ıntricular thrombus were identified by two experienced hocardiographers.

Imaging technique: Patients were studied with either a ırian V-3000 electronic phased array ultrasonoscope or a ɔrtable Advanced Technology Laboratory (ATL) Mark III echanical ultrasonoscope. A 2.5 megahertz transducer was utinely used with the Varian V 3000 and a 3 megahertz ınsducer with the ATL Mark III. A systematic examination ıs performed utilizing parasternal, apical and subcostal oustic windows with varying sector orientations.[8] The apical ecordial window was most useful in detecting left ventricular rombus because most such thrombi occurred at the apex. ɔr the apical views patients were examined with the head ghtly elevated and in the left lateral decubitus position with e transducer placed at the point of maximal impulse. With the echocardiographic beam directed toward the left atrium, routine two and four chambered views were obtained.[9] To provide a thorough examination of the apex, positions intermediate between these two standard sector orientations as well as an apical short axis view (Fig. 1) were also obtained. Shallow depth of field settings of 7 and 9 cm for the apical views with the mechanical sector scanner were particularly helpful in defining apical anatomy. We found the mechanical scanner superior to the phased array ultrasonoscope for defining apical anatomy because near field artifact was minimal and adequate resolution maintained. Multiple gain and reject settings were also utilized to ensure definition of the pericardium, epicardium, endocardium, and thrombus margin.

Diagnostic classification of left ventricular thrombus (Table I): Detection of left ventricular thrombus with two dimensional echocardiography depends upon the quality of the examination. We developed a grading scale that incorporates the quality of the examination in classifying the index of suspicion for left ventricular thrombus (Table I). The scale ranges from 0 to 4. *Grade 0* indicates a good quality examination of the left ventricle with no evidence for thrombus. Left ventricular echo densities may be present, but must have characteristics of ventricular structures other than thrombus. Such structures include the papillary muscles, muscle trabeculae and chordal structures. *Grade I* indicates an examination with an echo density in the left ventricle that is believed to be papillary muscle, muscle trabeculae or chordal structures rather than thrombus. However, the technical quality of the examination is not ideal, and does not permit a 0 grade. *Grade II* represents an examination with a definite echo density with nonspecific features present in the left ventricle. The quality of the examination or the nonspecific character of the echo mass prohibits further categorization. *Grade III* represents an examination demonstrating an echo density in the left ventricle highly suspicious of thrombus, but the quality of the



GURE 1. Patient 22. Apical short axis view of echocardiogram (**left**) obtained 7 days after acute anterior myocardial infarction. Artist's drawing at **right.** A large protruding apical thrombus (**arrows**) is present and demonstrates increased echo density compared with that of surrounding ɣocardium. A small pericardial effusion (PE) is also present. LV = left ventricular cavity; RV = right ventricular cavity.

TABLE I

Two Dimensional Echocardiographic Classification for Suspicion of Left Ventricular Thrombus

Class	Criteria
0	Thrombus definitely not present; technically good examination.
I	Definite left ventricular echo mass but probably not thrombus; examination technically not good enough to classify as 0 (probably represents cardiac structure other than thrombus).
II	Definite abnormality, but of uncertain nature.
III	Findings highly suspicious for thrombus; examination technically not adequate to classify as diagnostic.
IV	Findings characteristic of thrombus; technically good or adequate examination.

examination does not allow definitive characterization. *Grade IV* indicates an examination characteristic for left ventricular thrombus. An echo-dense left ventricular mass is present that is discrete from the endocardial surface and has other characteristics of thrombus (Table II).

Results

Of the 41 patients identified as having left ventricular thrombus on two dimensional echocardiography, 16 had a grade IV examination. In 11 of these 16 patients thrombus was confirmed with angiography, surgery, postmortem examination or serial two dimensional echocardiographic studies (Table III). In addition, in 9 of the 25 patients whose examinations were judged highly suggestive of thrombus (grade III), thrombus was also confirmed (Table III). Although none of the remaining 16 patients with highly suggestive examinations were shown to have a false positive study, they are not discussed further because positive confirmation was not obtained.

The observations presented in this report are thus based on the echocardiographic findings of 25 patients—16 with characteristic two dimensional echocardiographic examinations for thrombus and 9 patients with highly suggestive examinations whose diagnosis of thrombus was confirmed either by independent means or by serial two dimensional echocardiograms.

Documentation of Thrombus

Left ventricular angiography: In seven patients left ventriculography demonstrated apical filling defects consistent with thrombus[10] within 1 week of the two dimensional echocardiogram (Table III). In another three patients with a large left ventricular aneurysm ventriculograms were interpreted as negative for thrombus although the two dimensional echocardiogram indicated thrombus (grade III in one and grade IV in two). All three patients underwent aneurysmectomy within 48 hours of the positive echocardiographic study and thrombus was confirmed in each.

Surgery: Six patients had a surgical procedure that confirmed or supported the echocardiographic diagnosis of left ventricular thrombus (Table III). Three had left ventricular aneurysmectomy, and thrombus was confirmed in the aneurysmal segment in each. The remaining three patients had operative findings that supported the clinical and echocardiographic diagnoses of left ventricular thrombus. One had a left femoral arterial embolectomy 4 days after acute anterior myocardial infarction, and left ventriculography confirmed the presence of thrombus. After embolectomy this patient was placed on anticoagulant therapy and serial two dimensional echocardiographic studies demonstrated resolution of the thrombus. Another patient with recent transmural inferior myocardial infarction presented with evidence of acute occlusion of the right femoral artery. After embolectomy, anticoagulant therapy was not instituted and the patient returned several months later with multifocal transient cerebral ischemic attacks followed by a right-sided cerebrovascular accident. Further two dimensional echocardiography demonstrated a persistent left ventricular mass highly suggestive of thrombus. Another patient with long-standing congestive cardiomyopathy experienced severe abdominal pain while hospitalized for congestive heart failure. Exploratory laparotomy demonstrated a discrete segment of infarcted small bowel, and an embolus was removed from the superior mesenteric artery.

TABLE II

Two Dimensional Echocardiographic Features of Left Ventricular Thrombus

1. Associated wall motion abnormality.
2. Apical location frequent but not exclusive.
3. Distinct thrombus margin.
4. Acoustically distinct from underlying myocardium.
5. Free motion of an intracavitary thrombus margin.
6. Variation noted on serial examination.

Postmortem examination: Postmortem examination confirmed left ventricular thrombus in four patients with a positive echocardiographic examination (grade III in one and grade IV in three, Table III). Two patients had a recent anterior myocardial infarction and the other two had congestive cardiomyopathy.

Serial two dimensional echocardiographic studies: Serial echocardiographic evaluation was helpful in diagnosing a left ventricular mass as thrombus in seven patients. In four of these patients, the left ventricular mass thought to represent thrombus disappeared during follow-up studies while they were receiving anticoagulant therapy (Table III). In two of these four left ventriculography at the time of the initial positive echocardiographic study also confirmed thrombus. In another three patients, left ventricular thrombus developed during serial evaluation during the course of an acute anterior myocardial infarction.

Thrombi without independent confirmation: Of the 16 patients whose two dimensional echocardiograms were characteristic of thrombus (grade IV), 11 had thrombi that were documented by an independent technique or serial echocardiography. The five patients without further documentation of thrombus were also included in these observations because of unequivocal

hocardiographic features of left ventricular thrombus Table III, Fig. 1 to 5). Three were imaged during the urse of acute anterior myocardial infarction while the maining two had congestive cardiomyopathy.

chocardiographic Characteristics and Associated ndings of Left Ventricular Thrombus

Wall motion abnormalities: All patients had wall otion abnormalities adjacent to their thrombus. Wall otion was hypokinetic in two patients with congestive rdiomyopathy. Akinesia was noted in the remaining ree patients with congestive cardiomyopathy as well in several patients with ischemic heart disease. yskinesia (systolic expansion) of a segment of the ntricular wall adjacent to the thrombus was common. most patients with dyskinesia, the diastolic contour the ventricle was normal; in six patients the diastolic contour was clearly abnormal because of an expanded wall segment, and all six had a left ventricular aneurysm. Three of the six underwent successful left ventricular aneurysmectomy; two others died and both had an aneurysm containing thrombus confirmed at postmortem examination. In the remaining patient congestive cardiomyopathy developed with a persistent but markedly smaller mural thrombus at the 1 year follow-up study.

Location of thrombus: Twenty-three patients had thrombus located at the apex and all thrombi were imaged by the apical acoustic window. Two patients had thrombus located along the inferior wall; one in an area of akinesia and the other in a pseudoaneurysm.

Relation to left ventricular wall: The relation of thrombus to the endocardial surface and left ventricular cavity was also analyzed (Table III). Thrombi could be

ABLE III

linical and Echocardiographic Features of 25 Patients With Positive Confirmation of eft Ventricular Thrombus

Index of Suspi- ise cion*	Age (yr) & Sex	Wall Motion at LVT Site	Under- lying Heart Disease	Site of Infarct	Mural vs. Protruding	Confirmation
3	56M	A	IHD, AMI	Anterior	Protruding	LV angiography
3	57M	Slight dys	IHD, AMI	Anterior	Mural	LV angiography
3	38M	Slight dys (small LVA)	IHD, AMI	Anterior	Mural	LV angiography
4	54M	Dys	IHD, AMI	Anterior	Mural†	OH surgery
4	56M	Dys	IHD, Pseudo LVA	Inferior	Mural	OH surgery
3	56M	Dys	IHD, LVA	Anterior	Mural	OH surgery
4	55M	A	IHD, AMI	Anterior	Protruding	EM surgery Serial follow-up evaluation after LV angiography
3	64M	A	IHD, RMI	Inferior	Protruding	EM surgery
3	79M	Hypo	CCM	None	Protruding	EM surgery
3	65M	Dys	IHD, AMI	Anterior	Mural	Postmortem study
4	72M	Dys	IHD, LVA	Anterior	Mural‡	Postmortem study
4	72M	A	CCM, Mild AS	None	Protruding	Postmortem study; LV angiography
4	19M	Hypo	CCM, hyperthyroid	Anterior§	Mural Protruding	Postmortem study
4	42M	Dys	IHD, AMI	Anterior	Mural	Resolution on serial follow-up after detection
4	62M	A	IHD, AMI	Inferior	Mural	Resolution on serial follow-up after detection; LV angiography
3	50M	A	IHD, AMI	Anterior	Protruding	Resolution on serial follow-up after detection; LV angiography
4	68M	A	IHD, AMI	Inferior	Protruding	Resolution on serial follow-up after detection
4	58F	Dys	IHD, AMI	Anterior	Mural‡	Serial follow-up before and after detection
4	52M	Slight dys	IHD, AMI	Anterior	Mural	Serial follow-up before and after detection
4	45M	Slight dys	IHD, AMI	Anterior	Mural	Serial follow-up before and after detection
4	66M	Dys	IHD, LVA	Anterior	Mural‡	None
4	32M	Dys	IHD, AMI	Anterior	Protruding†	None
4	78M	Dys	IHD, AMI	Anterior	Mural† Protruding	None
4	57M	A	IHD, CCM	Inferior	Mural‡	None
4	56F	A	CCM, S/P MVR	Anterior None	Protruding Protruding†	None

* 3 = highly suspicious; 4 = diagnostic. † Free intracavitary motion of thrombus margin. ‡ Layering noted on two dimensional echocardiography. farction after initial detection of thrombus on two dimensional echocardiography
A = akinesia; AMI = acute myocardial infarction; AS = aortic stenosis; CCM = congestive cardiomyopathy; CVA = cerebrovascular accident; s = dyskinesia; EM = peripheral embolectomy; Hypo = hypokinesia; IHD = ischemic heart disease; LV = left ventricular; LVA = left ventricular eurysm; LVT = left ventricular thrombus; OH = open heart; RMI = recent myocardial infarction; S/P MVR = status postmitral valve replacent.

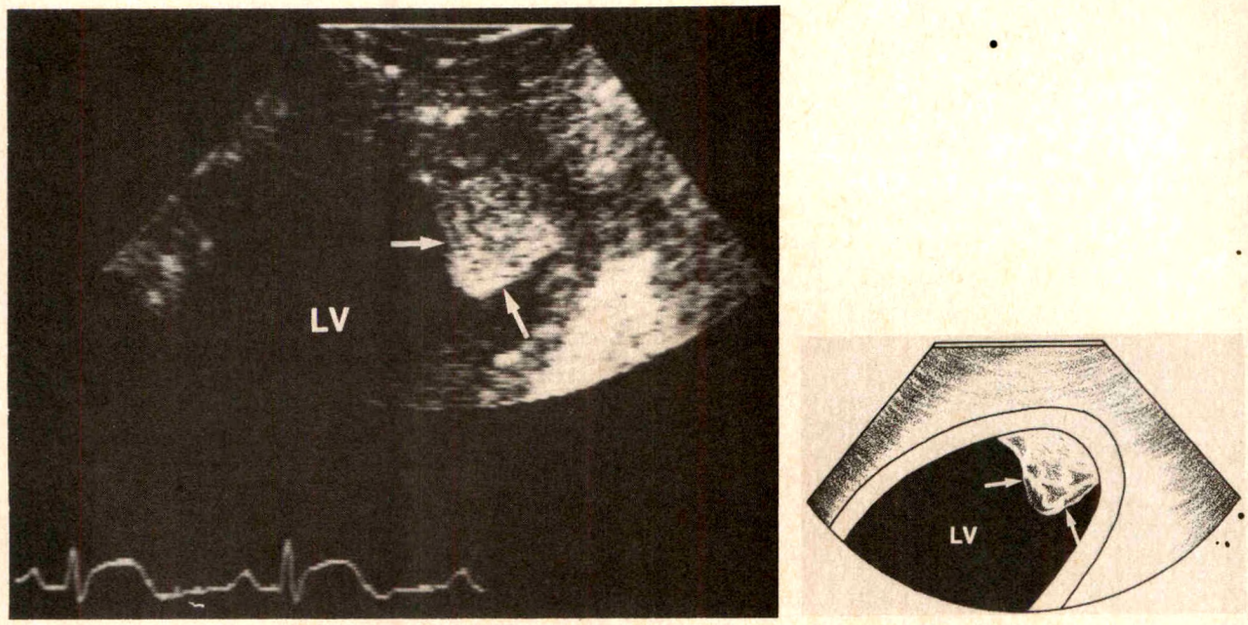


FIGURE 2. Same patient as in Figure 1. Apical two chambered view at shallow range setting demonstrating a discrete protruding left ventricular thrombus (**arrows**). Abbreviations as in Figure 1.

classified as mural (Fig. 6) or protruding (Fig. 1 and 2). Flat thrombi parallel to the endocardial surface were classified as mural, and thrombi that projected into the left ventricular cavity as protruding. These classifications were not mutually exclusive; three patients had evidence of both patterns. Of the remaining 22 thrombi, 13 were mural and 9 protruding.

The echocardiographic dimensions of the protruding thrombi varied, with the smallest detected thrombus measuring 1.5 by 1.5 by 2.5 cm (Table III, Patient 17). The dimensions of mural thrombi were more difficult to quantitate because of their wide area of contact with the endocardial surface. The smallest thickness of an identified mural thrombus was approximately 1 cm (Table III, Patient 6).

Motion of the intracavitary thrombus margin: Only four patients had evidence for free intracavitary motion of a thrombus margin. Two of these four patients had a thrombus with ragged margins that moved in a limited fashion in the left ventricular cavity during the cardiac cycle (Fig. 4). The portions with free motion were of the same echo density as the remainder of the

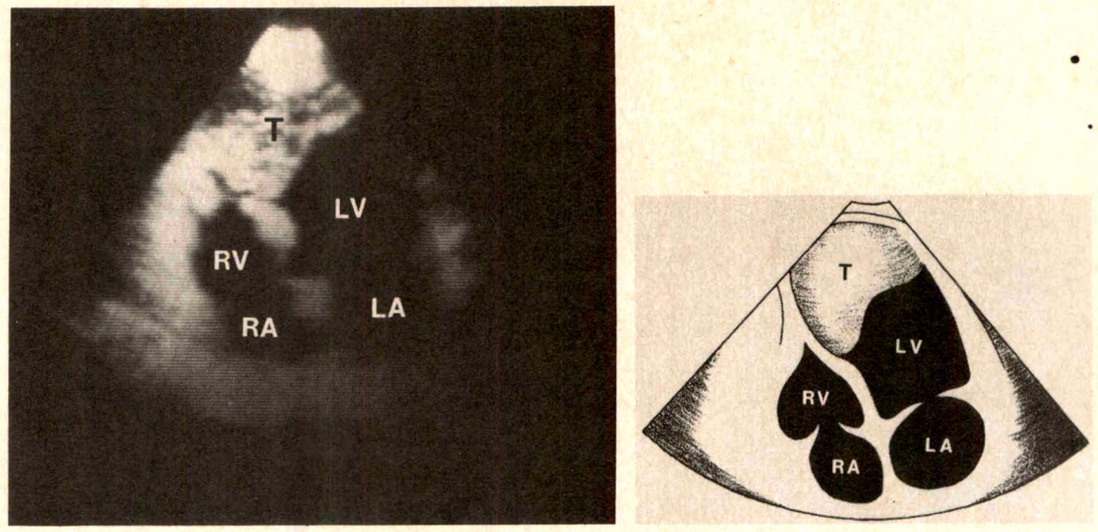
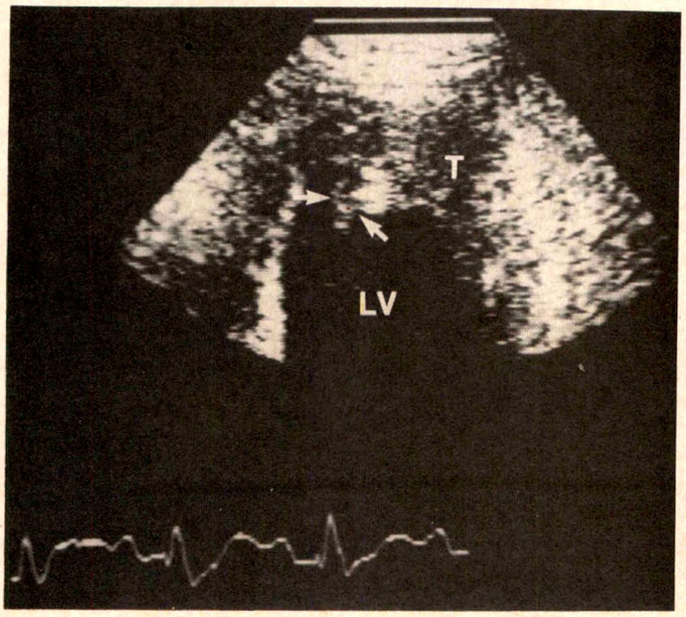


FIGURE 3. Patient 21. Apical four chambered view of echocardiogram demonstrating a large mural thrombus (T) 10 days after acute anterior infarction. Note the distortion of the apical contour indicating aneurysm formation. LA = left atrium; RA = right atrium; other abbreviations as in Figure 1.



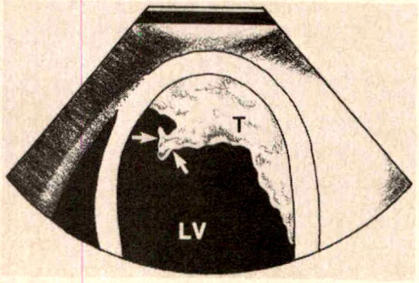


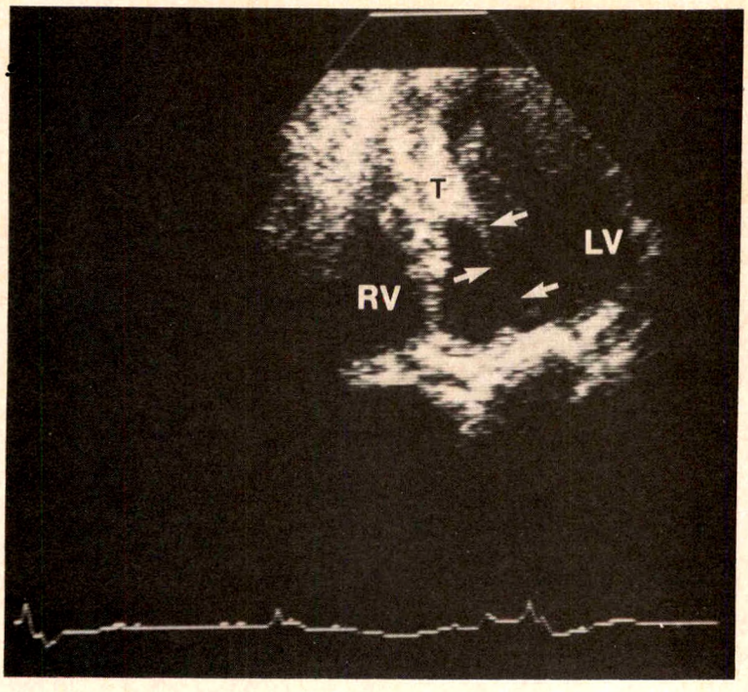
FIGURE 4. Patient 23. Apical two chambered view at shallow range setting. A left ventricular thrombus (T) with evidence of free motion of an intracavitary margin is present. The portion of the thrombus indicated by the **arrows** demonstrated a limited degree of motion in the left ventricular cavity (LV). This portion of the thrombus is of the same echo density as the remainder of the thrombus.

hrombus. Two other patients had a thrombus that demonstrated a different type of free intracavitary motion. In these two, large dynamic masses of low amplitude echoes were present in the left ventricular cavity and appeared associated with a discrete thrombus (Fig. 5). These masses had a veil-like appearance and swirled in the left ventricular cavity.

Echo density of intracavitary thrombus margin: Several patients demonstrated evidence of a layered thrombus with variations in echo density. In these patients the most echo-dense layer of thrombus was adjacent to the left ventricular cavity (Fig. 6) and ranged from 2 to 5 mm in thickness. Each of these patients had a mural pattern.

Comment

An increasing amount of evidence[11–17] indicates that two dimensional echocardiography is a useful and perhaps the preferred method of detecting left ventricular thrombus. These data and our present results indicate that two dimensional echocardiography allows detection of left ventricular thrombi that might not be clinically manifest or detected by other available methods. It is apparent that two dimensional echocardiography has



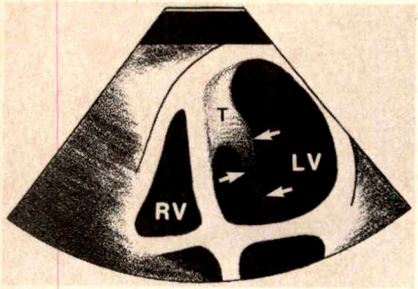
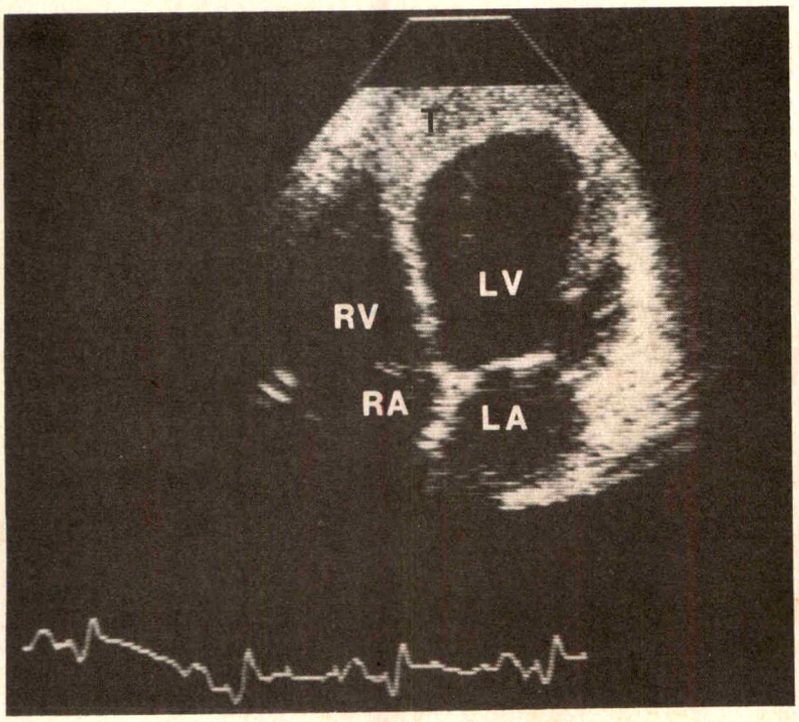


FIGURE 5. Patient 25. Apical two chambered view. A protruding thrombus (T) is present at the apical-septal junction. A large swirling mass of low density echoes (**arrows**) that moved freely in the left ventricle is also present. Abbreviations as in Figure 1.



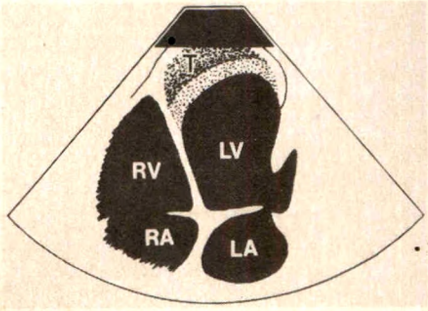


FIGURE 6. Patient 11. Apical four chambered view demonstrating a mural thrombus (T) with layering. A layer approximately 5 mm thick adjacent to the left ventricular (LV) cavity is present and of increased echo density when compared with the remainder of the thrombus. Abbreviations as in Figures 1 and 3.

the potential to provide previously unavailable information regarding the natural history and response to therapy of left ventricular thrombi. Such information will ultimately enhance our understanding of left ventricular thrombi; however, this ability to identify thrombi raises important questions regarding patient management and therapy. Hence, every precaution should be taken to ensure the accuracy of the diagnosis of thrombus by this technique.

Although the reliability of two dimensional echocardiography has been established, guidelines for accurate diagnosis and steps to avoid a false-positive diagnosis have not been stressed. In this report we summarize various two dimensional echocardiographic characteristics and associated features of left ventricular thrombus in 25 patients. In addition, we discuss potential causes of a false positive diagnosis and ways of avoiding these errors.

Two Dimensional Echocardiographic Features of Left Ventricular Thrombus (Table II)

Associated wall motion abnormality: Relative stasis of blood in areas of abnormal wall motion and endocardial injury have been implicated in the genesis of left ventricular thrombus.[1] Pathologic evidence of left ventricular wall abnormalities adjacent to thrombus has been noted,[1] and wall motion abnormalities have been observed angiographically in patients with left ventricular thrombus.[10] In our experience thrombus in the left ventricle is *always* associated with wall motion abnormalities. However, wall motion abnormalities associated with thrombus varied from generalized hypokinesia in patients with congestive cardiomyopathy to frank dyskinesia in patients with left ventricular aneurysm. We are reluctant to consider the diagnosis of left ventricular thrombus in the absence of some wall motion abnormality.

Twenty-one of our patients had ischemic heart disease, with prior myocardial infarction and wall motion abnormalities. Sixteen had anterior and five had inferior infarction. This association of anterior infarction and thrombus is consistent with previous pathologic,[1] angiographic[10] and echocardiographic[12–14] reports. Three of the five patients with inferior infarction had a thrombus at the apex, and each of these three had apical wall motion abnormalities. The other two patients had definite inferior wall abnormalities where the thrombus was located.

Thrombus location: Previous autopsy studies[1–3] have indicated that left ventricular thrombus is most frequently located at the apex. In 23 of our 25 patients left ventricular thrombus was at the apex; in the remaining 2 it was located along the inferior wall. The predilection for thrombus formation at the apex suggests that abnormal wall motion in this area results in a greater focal stasis of intracavitary blood than does comparable wall motion abnormality in other areas of the ventricle. Of importance from a technical aspect was the fact that all thrombi were imaged from the apical acoustic window. In contrast to observations made by Meltzer et al.,[13] we have found that the left ventricular apex cannot routinely be adequately examined by the subcostal window, although this approach may support or confirm findings noted on apical views.

Distinct thrombus margin: The identification of thrombus and its relation to the endocardial surface is obvious in some cases (Fig. 1), but in many cases the distinction is more difficult, particularly when a mass

ıat is not obviously thrombus is imaged at the left entricular apex. In these cases an attempt should be ıade to identify pericardium, epicardium, endocardium ıd thrombus margins. An accurate assessment of these ;ructures at the left ventricular apex can be challeng-ıg, particularly in the setting of a segmental wall ab-ormality. Multiple gain and reject settings will aid in lentifying apical anatomy, but in our experience the ıost useful technique employs shallow depth settings rovided that near field artifact is minimal and ade-ıate resolution maintained. We have found the me-ıanical scanner superior to the phased array ultraso-ɔscope in obtaining high resolution imaging of the ɔex. Proper identification of the pericardium is helpful nce it establishes a landmark. The pericardium is latively stationary at the apex and may be separated om the epicardium by an echo-free space when peri-ırdial fluid or thickening is present (Fig. 1). Apical wall ɔicardial and endocardial surfaces move in a parallel shion during the cardiac cycle when imaged from the ɔical window, although varying degrees of systolic ıickening or thinning be noted.

Wall thickness should be assessed particularly in the tting of left ventricular aneurysm. Usually the walls a discrete aneurysm are thin; hence, the finding of ɔrmal wall thickness in an aneurysmal segment should ise the suspicion of mural thrombus.[12] Careful ex-nination of the apex with shallow depth settings may ıen allow accurate distinction of thrombus from en-ɔcardium. Another difficulty in identifying thrombus argins related to width of the ultrasonic beam. Be-use the beam has a certain width, it is possible to ob-in images of adjacent myocardium within the left ntricular cavity.[18] In our experience, these spurious hoes are common with wall motion abnormalities, rticularly when echo-dense myocardial scar is sent. Such spurious echoes can simulate the margins a thrombus. Correct identification of these echoes as tifact can be made by obtaining multiple views to nfirm apical contour and anatomy.

Acoustic characterization of thrombus: Although e acoustic characteristics of thrombi may differ, the ho density of thrombi is usually greater than that of ljacent myocardium.[14] We observed that protruding rombi tend to be relatively echo-dense (Fig. 1 and 2) ıile mural thrombi in general tend to be less echo-ense (Fig. 6) and hence cause more difficulty in dis-nguishing thrombus from myocardium. Individual rombi may have heterogenous areas of echo density at occasionally give the appearance of a layered pat-rn. When a layered pattern is observed, the most ho-dense portion of the left ventricular thrombus is ually along the intracavitary margin (Fig. 6). This area esumably represents the most recently formed por-ɔn of the thrombus. Perhaps the composition or ar-itecture of recently formed thrombus results in a eater echo density than that of older thrombus. In pport of this concept is the imaging of highly echo-nse thrombi within 10 days of acute transmural in-rction in 10 of our 25 patients. The portion of the rombus between the intracavitary border and endo-rdium should be echo-dense in comparison with in-tracavitary blood unless a portion of the thrombus has liquified. If liquification of a portion of the thrombus has occurred, then an echo-free space may be present within the substance of the thrombus.

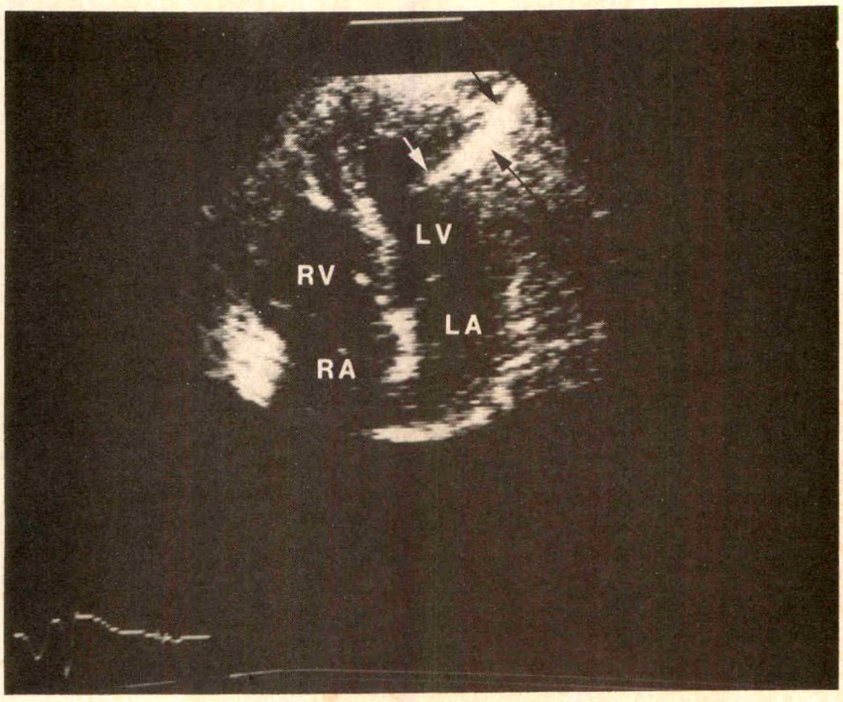
Intracavitary motion of thrombus margin: Unrestricted motion of an intracavitary thrombus margin[13,14] has not been common in our experience and occurred in only 4 of our 25 patients. In two of the four, a small ragged portion of the thrombus along the intracavitary border showed limited motion within the left ventricular cavity (Fig. 4). Because this pattern of motion has not been observed in any other circumstance, it may aid in correctly identifying an echo mass as thrombus. The other two patients demonstrated a large, low density swirling mass of intracavitary echoes in addition to a discrete thrombus (Fig. 5). The origin of these swirling echoes is not clear. We have noted similar echoes in cases where no discrete thrombus was identified; hence they may represent a phenomenon related to early thrombus formation or even low flow. In any event their presence should prompt a thorough search for discrete thrombus. Both patterns of intracavitary motion associated with these thrombi were easily distinguished from chordal structures, papillary muscles and vegetative lesions.

Variation noted on serial studies: Observations made during serial two dimensional echocardiographic studies of patients with a left ventricular mass have been helpful in identifying the mass as thrombus. The complete disappearance of a mass on serial examinations, as noted in four patients on chronic anticoagulant therapy, or the development of an echo-dense mass with characteristics of thrombus during acute myocardial infarction, as noted in three patients, provides support for the diagnosis of left ventricular thrombus.

Although the echocardiographic features of a left ventricular mass may be obviously characteristic of thrombus, there are instances where these features are not specific or the quality of the images is suboptimal and hence the examination cannot be considered characteristic for thrombus. We have used a grading scale to indicate our index of suspicion for left ventricular thrombus. This grading scale (Table I) incorporates the echocardiographic features of or associated with left ventricular thrombus (Table II) as well as a subjective evaluation of the quality of images obtained. This classification system provides a practical method of conveying the index of suspicion for thrombus and a convenient method for prospectively examining diagnostic accuracy. We have been pleased with the diagnostic accuracy of examinations classified as highly suggestive or characteristic of left ventricular thrombus and the lack of false positive interpretations to date. Although this particular approach may be unique for our laboratory, we believe it is most important for laboratories to evaluate on an ongoing basis their accuracy in this difficult area of two dimensional echocardiographic interpretation.

Avoidance of False Positive Studies

False positive examinations may be the result of either problems inherent in the ultrasonic technique itself



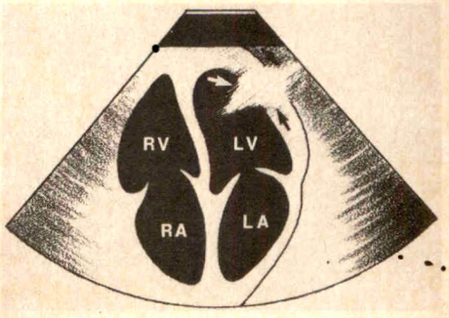
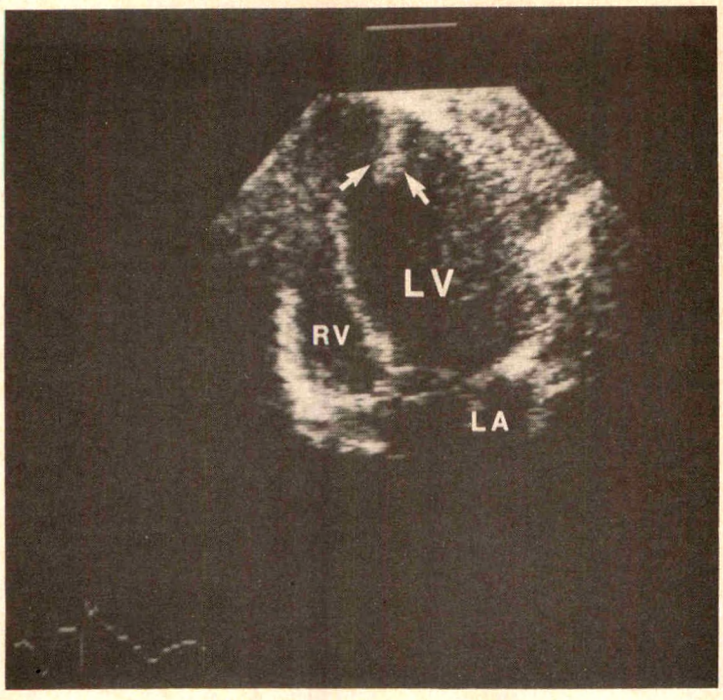


FIGURE 7. Apical two chambered view demonstrating a strong echo reflector along the distal lateral wall (**arrows**) which causes a spurious intracavitary echo simulating a thrombus margin. Abbreviations as in Figures 1 and 3.

or errors in correctly identifying normal or pathologic structures at the left ventricular apex.

Ultrasonic technique and current instrumentation: Apical views are most useful in diagnosing left ventricular thrombi. The apex is only a few centimeters from the source of ultrasound in these views; hence, axial and lateral resolution in the near field are most important. Near field artifact, frequently a problem with phased array systems, must be minimized; otherwise, low gain settings are necessary and may not permit recognition of low reflective structures such as the endocardial surface or thrombus margin. In addition, spurious intracavitary echoes caused by structures outside the main axis of the ultrasonic beam can also cause considerable interpretative difficulty (Fig. 7).[18] This problem can frequently be solved by obtaining multiple sector orientations of the area in question. A true intracavitary echographic target such as a throm-



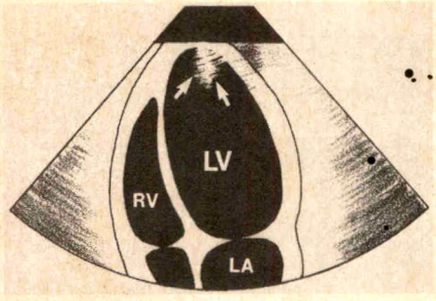
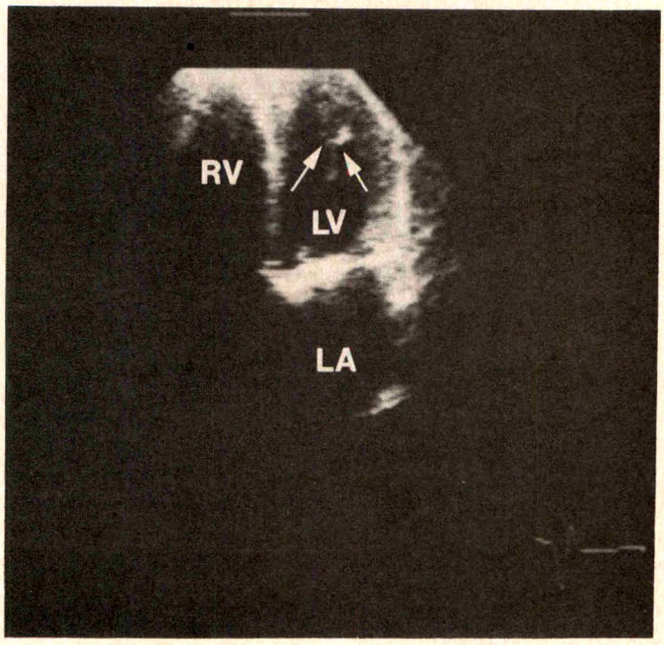


FIGURE 8. Apical four chambered view of a patient with previous infarction. Reverberation artifact from the apex is present (**arrows**) which simulates a protruding intracavitary thrombus. Arrows indicate this reverberation artifact. Abbreviations as in Figures 1 and 3.



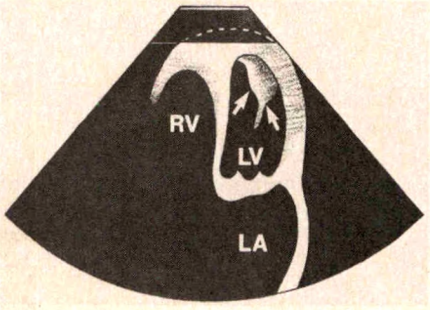
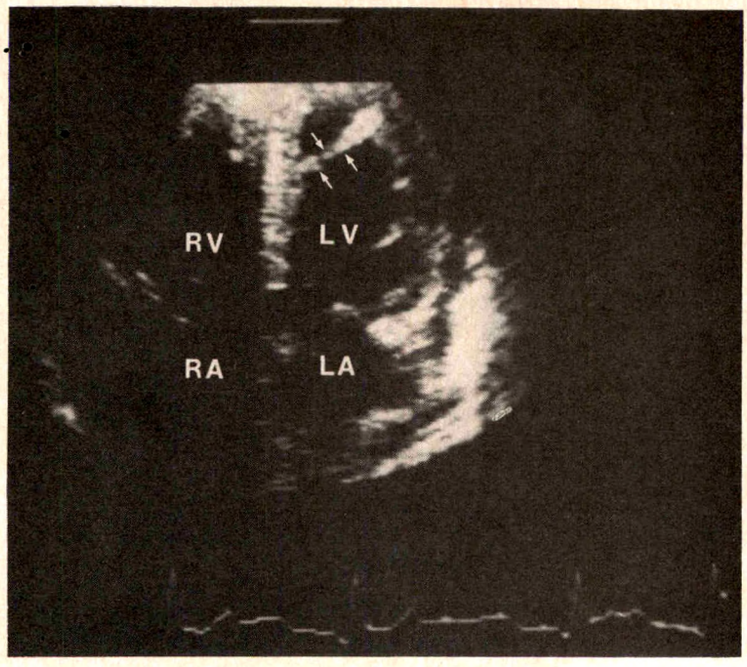


FIGURE 9. Apical two chambered view of a patient after mitral valve replacement. A partially amputated papillary muscle with chordal remnants is present (**arrows**) and simulates a thrombus. However, it is in the position of the papillary muscle, and no wall motion abnormality was present. Abbreviations as in Figures 1 and 3.

ıs or thrombus margin should have a constant and producible position in the left ventricular cavity, ıereas spurious echoes will show a change in position disappear when the sector orientation is altered. Very flective echographic targets such as an area of calcified yocardial scar can also be troublesome, not only be-use of lateral resolution difficulties caused by beam dth but also axial resolution problems secondary to verberation artifact (Fig. 8). These axial reverbera-ıns can usually be correctly identified since they ap-ar parallel to their source and exhibit parallel vertical tion. Again, changing acoustic window or sector or-ientation will be helpful in identifying these echoes as artifact.

Identification of normal or pathologic apical structures: Certain normal or pathologic structures, other than thrombus, may be located near the left ventricular apex and misconstrued as thrombus. Such structures include papillary muscles, muscle trabeculae, chordal structures and tangential left ventricular wall.

Papillary muscles: Papillary muscle identification usually causes little diagnostic dilemma. In the apical four chambered view, the posteromedial papillary



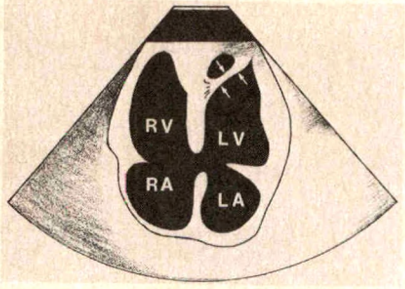


FIGURE 10. Apical four chambered view of a patient with left ventricular hypertrophy. A muscular bridge coursing from the lateral apical wall to the mid portion of the interventricular septum is noted (**arrows**). Note that an echo-free space is present on either side of this muscular bridge. Abbreviations as in Figures 1 and 3.

muscle appears along the septal aspect of the left ventricle near the junction of the middle and distal third of the interventricular septum. The anterolateral papillary muscle appears along the lateral left ventricular wall near the junction of the middle and distal third. When mitral valve replacement has been performed, a portion of the papillary muscles and their chordal structures may be partially amputated, and the remaining structures may be misinterpreted as thrombus (Fig. 9). A helpful finding in this situation is that the papillary muscles are located in their usual position and are not necessarily associated with left ventricular wall motion abnormality.

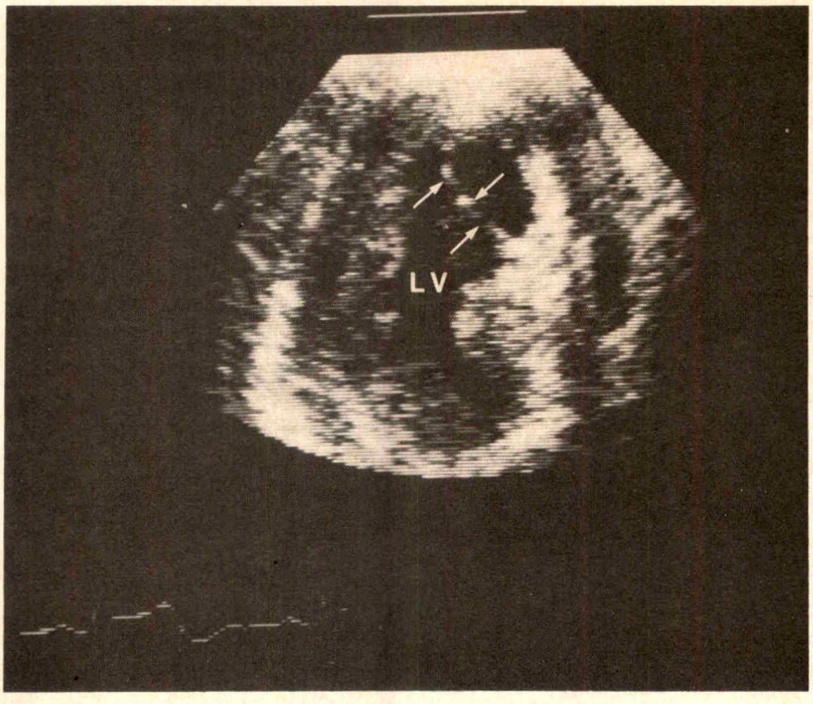
Muscle trabeculation: Heavy trabeculation at the apex frequently occurs with left ventricular hypertrophy and may present a confusing picture when attempting to examine the apex for possible thrombus. These trabeculations may appear as muscle bridges (Fig. 10) and can be present in any different arrangement in the left ventricle. Echo-free areas on each side on these bridges and lack of wall motion abnormality will aid in identifying these structures as trabeculation rather than thrombus.

Chordal structures: Chordal structures present in the left ventricle include true chordae tendineae and fine chord-like structures that interconnect muscle trabeculae. True chordae tendineae are imaged between the area of the papillary muscles and mitral valve leaflets and occasionally appear as bright fleeting echoes that dart into and out of the ultrasonic beam during the cardiac cycle. These echoes are discrete and may represent either diastolic buckling of individual chordae tendineae or echo planes perpendicular to different chordae during various portions of the cardiac cycle producing a fleeting echocardiographic pattern. The discrete nature of these echoes aids in their distinction from the low amplitude swirling masses of echoes occasionally associated with discrete left ventricular thrombus.

The chord-like structures connecting trabeculi can also be imaged in the left ventricle (Fig. 11). These have a fine string-like appearance with an echo-free area on each side. Both of these features aid in distinguishing these structures from thrombi. In addition, these chord-like structures are not necessarily associated with left ventricular wall motion abnormalities. However, they must be differentiated from the margin of a thrombus that has free intracavitary motion, and this distinction can be difficult. These chord-like structures are usually straightened during diastole but some buckling can occur with systole. In contrast, free margins of a thrombus assume varying positions during the cardiac cycle and demonstrate beat to beat variation in their motion (Fig. 5).

Tangential left ventricular wall: Occasionally tangential data will be obtained through normal ventricular muscle and simulate mural thrombus (Fig. 12). Complete examination with multiple sector orientations from the apical acoustic window will assist in correctly identifying these layered masses as tangential left ventricular wall rather than thrombus. This can also be a problem in sector planes parallel to the papillary muscle. Orientation of the echo plane parallel through a papillary muscle may simulate a mass protruding into the left ventricular cavity that can be confused with a protruding left ventricular thrombus.

In summary, left ventricular thrombi have certain characteristics in location, acoustic appearance and relation to underlying endocardium and myocardium that allow detection with two-dimensional echocardi-



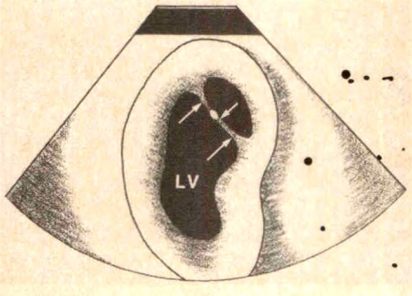
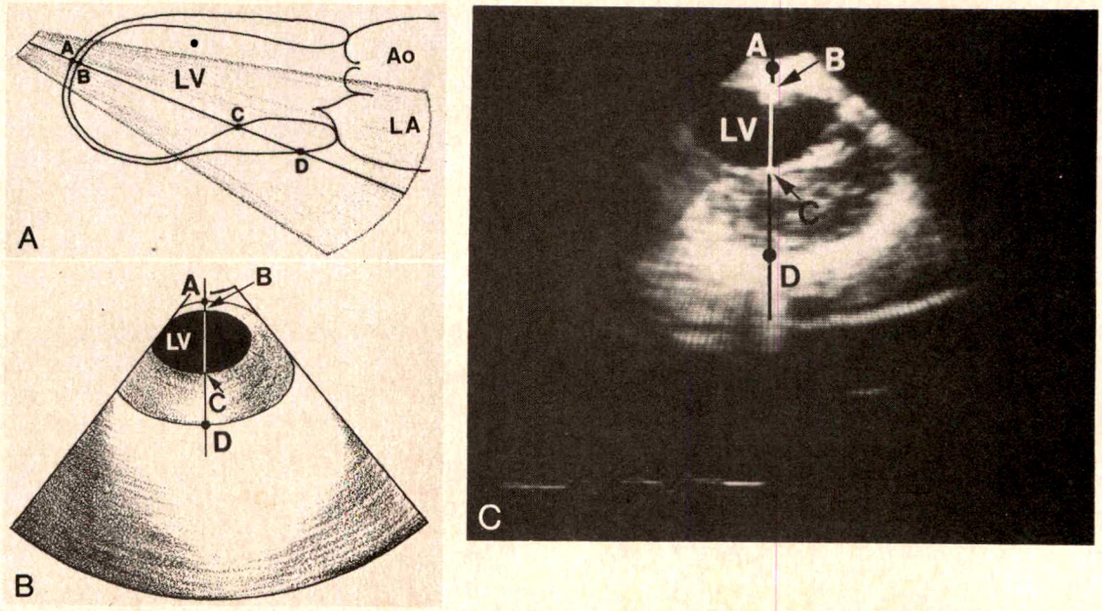


FIGURE 11. Apical cross-sectional view of a patient with left ventricular hypertrophy. A fine chordal structure is present (**arrows**) which courses across the apex. An echo-free space is present on either side of the string-like structure. LV = left ventricle.



GURE 12. A, diagram depicting an apical long axis view in a patient with an apical aneurysm. An echo plane that could be obtained from the apex also noted. The main axis of this echo plane intersects the aneurysmal epicardium at point A and its endocardium at point B. The apical plane somewhat tangential to the uninvolved inferior wall intersecting the endocardium at point C and epicardium at point D. **B,** diagram of the apical ne echocardiogram diagrammed in **A**. This plane is perpendicular to the aneurysm (A, B) but tangential to the normal inferior wall (C, D). The gential data from the inferior wall simulate a mural thrombus. **C,** still frame two dimensional image of a plane perpendicular to an aneurysmal cal segment but tangential to the normal inferior myocardial wall as depicted in **B**. These tangential data simulate a mural thrombus. Images ained by different sector orientations and acoustic windows can clarify the anatomy of the apex and avoid misinterpretation of tangential data thrombus. Ao = aorta; other abbreviations as in Figures 1 and 3.

raphy. This technique is clinically useful for detecting ft ventricular thrombi and appears more sensitive an angiography. Possible errors from misinterpretaon of spurious intracavitary echoes must be avoided. addition, papillary muscles, muscle trabeculae, ordal structures and tangential left ventricular muscle ust be correctly identified to avoid false positive inpretations.

Acknowledgment

We thank Charles Alexander, MD, Gary Hanovich, MD, Mark Sharon, MD, Vijender Arora, MD, Elliott Chesler, MD, Peter Kieley, MD, Bengie Goldfarb, MD and Thomas Mears, MD as well as the housestaff of Hennepin County Medical Center for referral of patients included in these observations. Barbara Nelson provided secretarial services.

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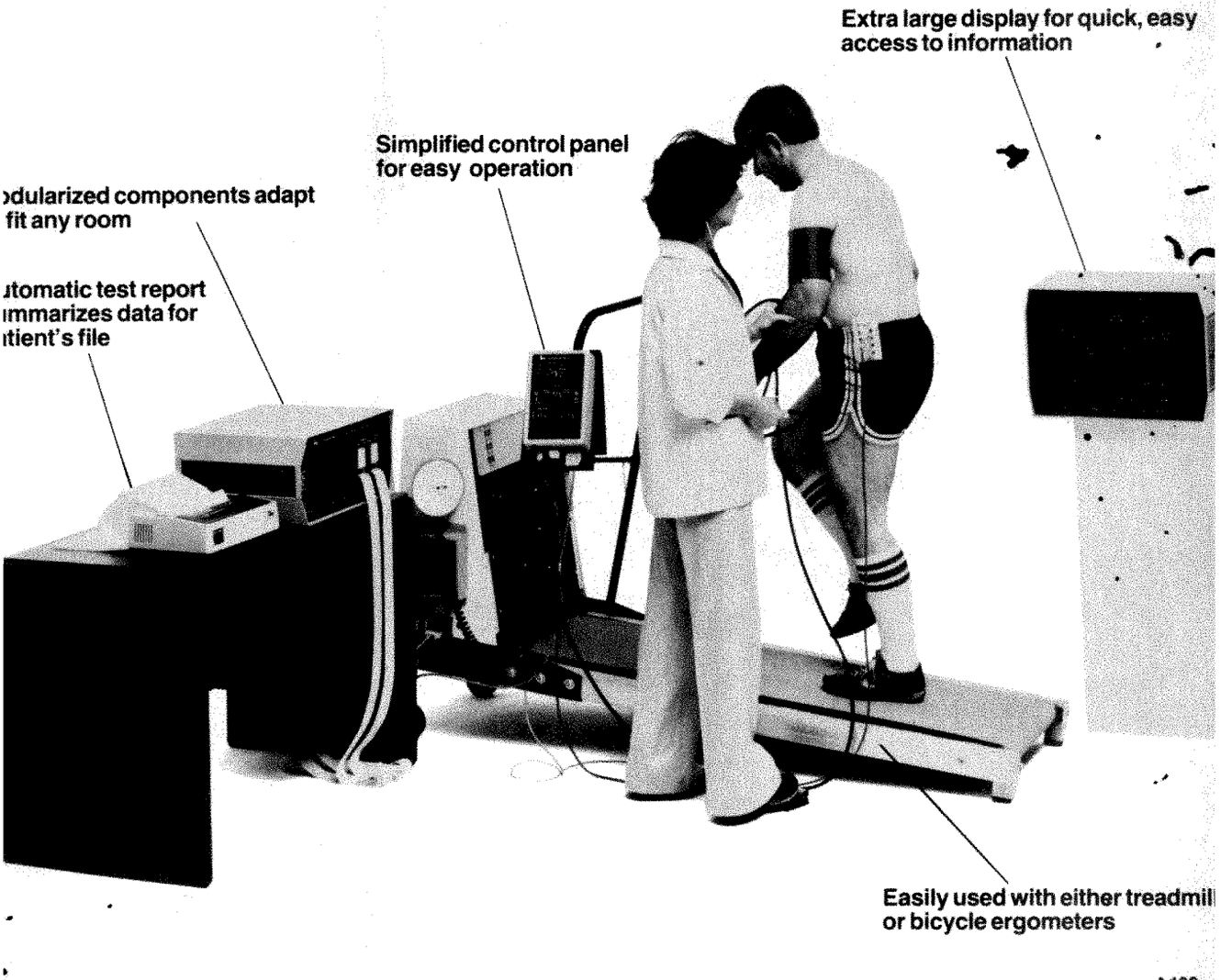

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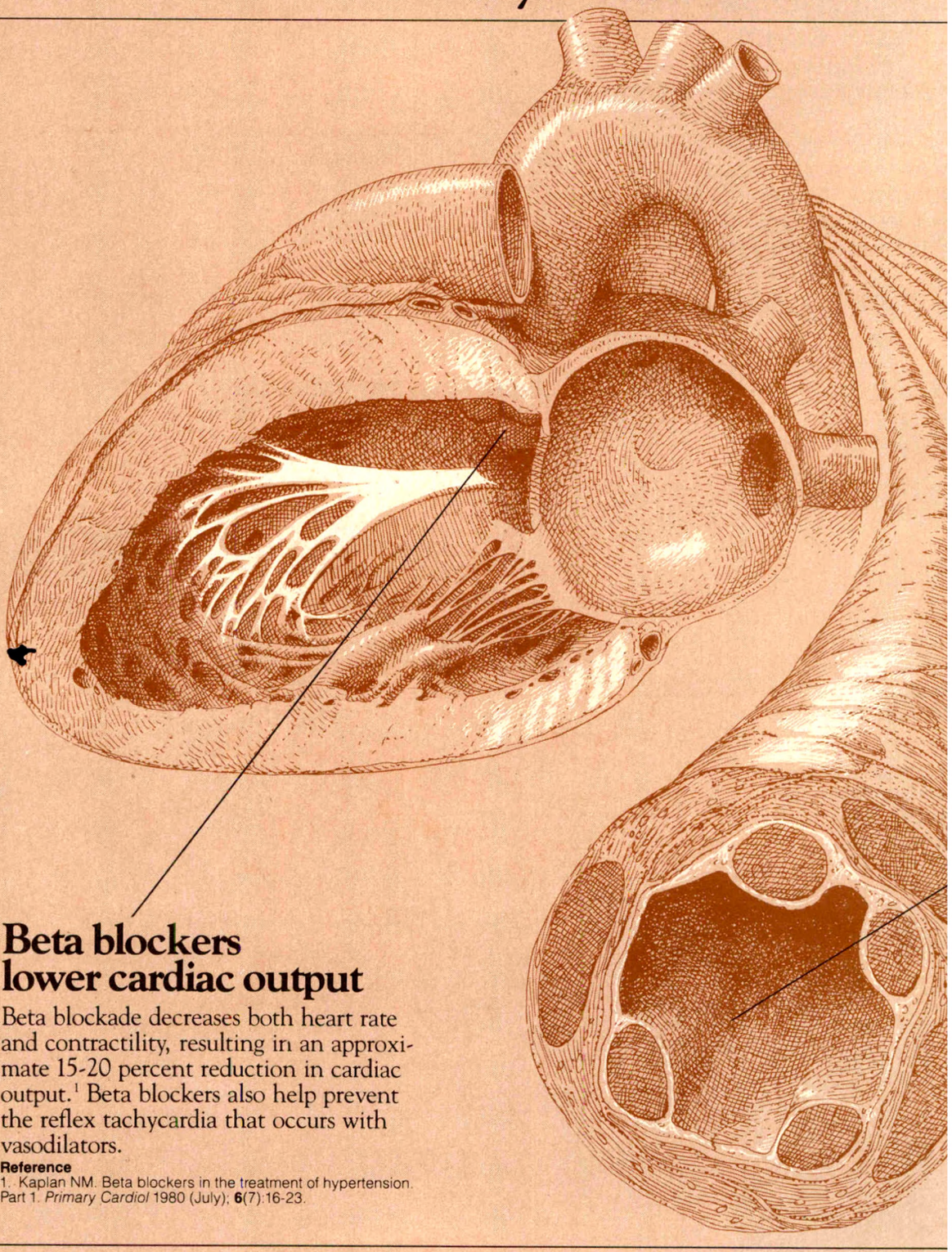
Apresoline
hydralazine



Beta blockers lower cardiac output

Beta blockade decreases both heart rate and contractility, resulting in an approximate 15-20 percent reduction in cardiac output.[1] Beta blockers also help prevent the reflex tachycardia that occurs with vasodilators.

Reference

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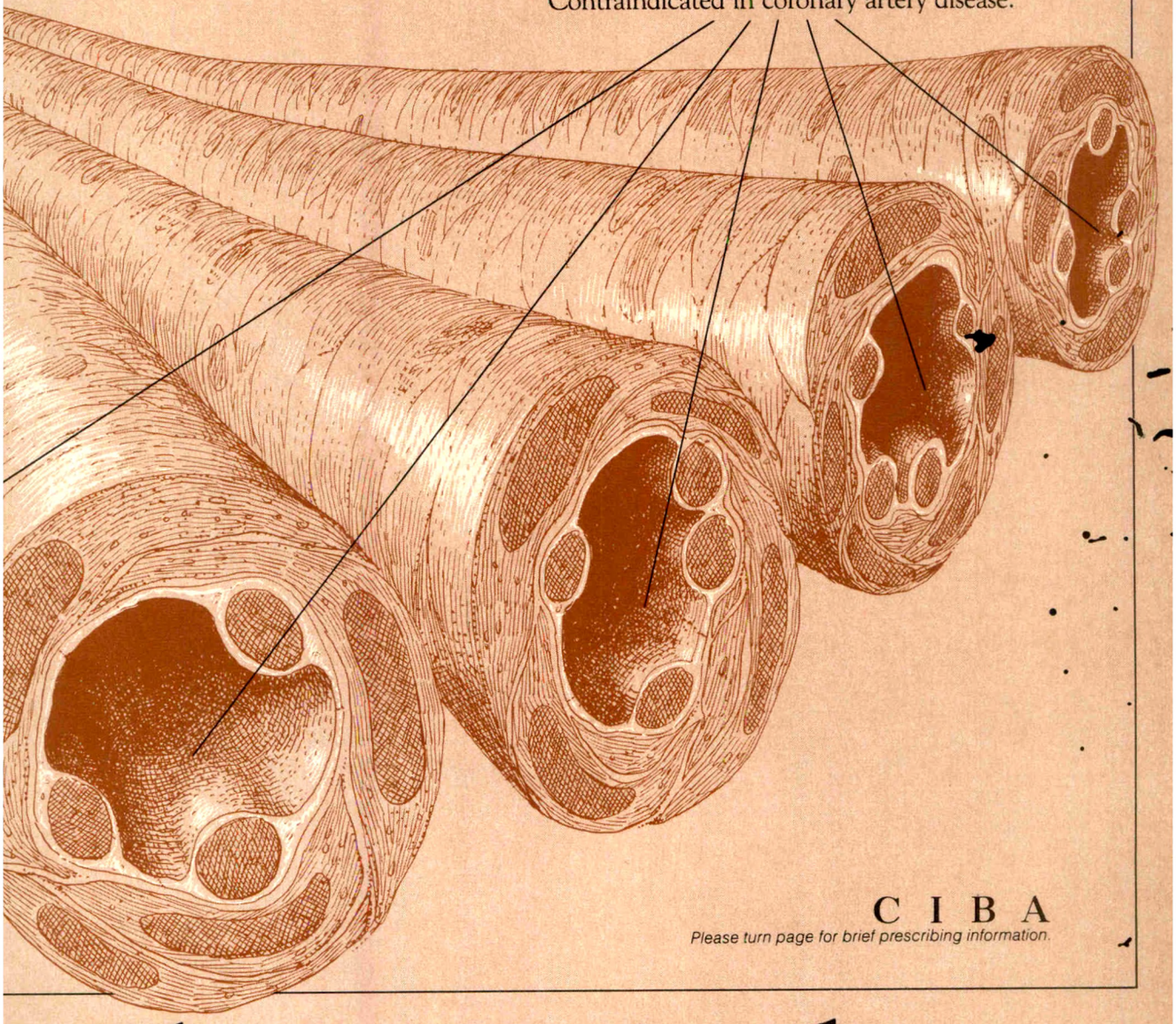

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ABLETS

DICATIONS

ssential hypertension, alone or as an adjunct.

ONTRAINDICATIONS

/persensitivity to hydralazine; coronary artery disease; and mitral ilvular rheumatic heart disease.

ARNINGS

/dralazine may produce in a few patients a clinical picture simulating ystemic lupus erythematosus. In such patients hydralazine should be scontinued unless the benefit-to-risk determination requires continued ntihypertensive therapy with this drug. Symptoms and signs usually gress when the drug is discontinued but residua have been detected any years later. Long-term treatment with steroids may be necessary. omplete blood counts, L.E. cell preparations, and antinuclear antibody er determinations are indicated before and periodically during pro- ged therapy with hydralazine even though the patient is asymptomatic. ese studies are also indicated if the patient develops arthralgia, fever, ieart pain, continued malaise or other unexplained signs or symptoms. positive antinuclear antibody titer and/or positive L.E. cell reaction quires that the physician carefully weigh the implications of the test sults against the benefits to be derived from antihypertensive therapy th hydralazine.

se MAO inhibitors with caution in patients receiving hydralazine.

nen other potent parenteral antihypertensive drugs, such as diazoxide, e used in combination with hydralazine, patients should be continu- sly observed for several hours for any excessive fall in blood pressure. ofound hypotensive episodes may occur when diazoxide injection and presoline (hydralazine hydrochloride) are used concomitantly.

sage in Pregnancy

imal studies indicate that hydralazine is teratogenic in mice, possibly rabbits, and not in rats. Teratogenic effects observed were cleft palate d malformations of facial and cranial bones. Although clinical perience does not include any positive evidence of adverse effects the human fetus, hydralazine should not be used during pregnancy less the expected benefit clearly justifies the potential risk to the fetus.

ECAUTIONS

/ocardial stimulation produced by Apresoline can cause anginal acks and ECG changes of myocardial ischemia. The drug has been plicated in the production of myocardial infarction. It must, therefore, used with caution in patients with suspected coronary artery disease. e "hyperdynamic" circulation caused by Apresoline may accentuate ecific cardiovascular inadequacies. An example is that Apresoline ay increase pulmonary artery pressure in patients with mitral valvular ease. The drug may reduce the pressor responses to epinephrine. stural hypotension may result from Apresoline, but is less common an with ganglionic blocking agents. Use with caution in patients with rebral vascular accidents.

hypertensive patients with normal kidneys who are treated with resoline, there is evidence of increased renal blood flow and a intenance of glomerular filtration rate. In some instances improved al function has been noted where control values were below normal or to Apresoline administration. However, as with any antihypertensive ent, Apresoline should be used with caution in patients with advanced al damage.

ripheral neuritis, evidenced by paresthesias, numbness, and tingling, s been observed. Published evidence suggests an antipyridoxine ect and the addition of pyridoxine to the regimen if symptoms develop. od dyscrasias, consisting of reduction in hemoglobin and red cell nt, leukopenia, agranulocytosis, and purpura, have been reported. If h abnormalities develop, discontinue therapy. Periodic blood counts advised during prolonged therapy.

e Apresoline tablets (10 and 100 mg) contain FD&C Yellow No. 5 rtrazine) which may cause allergic-type reactions (including bronchial hma) in certain susceptible individuals. Although the overall inci- nce of FD&C Yellow No. 5 (tartrazine) sensitivity in the general pulation is low, it is frequently seen in patients who also have aspirin persensitivity.

VERSE REACTIONS

verse reactions with Apresoline are usually reversible when dosage educed. However, in some cases it may be necessary to discontinue drug.

mmon: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; hycardia; angina pectoris.

ss frequent: Nasal congestion; flushing ; lacrimation; conjunctivitis; ripheral neuritis, evidenced by paresthesias, numbness, and tingling; ema; dizziness; tremors; muscle cramps; psychotic reactions charac- zed by depression, disorientation, or anxiety; hypersensitivity cluding rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, d, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; ralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, con- ting of reduction in hemoglobin and red cell count, leukopenia, agran- cytosis, and purpura; hypotension; paradoxical pressor response.

SAGE AND ADMINISTRATION

iate therapy in gradually increasing dosages; adjust according to ividual response. Start with 10 mg 4 times daily for the first 2 to ays, increase to 25 mg 4 times daily for balance of first week. For cond and subsequent weeks, increase dosage to 50 mg 4 times daily. maintenance, adjust dosage to lowest effective levels.

incidence of toxic reactions, particularly the L.E. cell syndrome, igh in the group of patients receiving large doses of Apresoline. few resistant patients, up to 300 mg Apresoline daily may be uired for a significant antihypertensive effect. In such cases, a lower sage of Apresoline combined with a thiazide, reserpine, or both may considered. However, when combining therapy, individual titration is ential to insure the lowest possible therapeutic dose of each drug.

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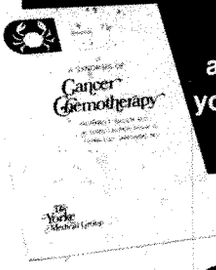

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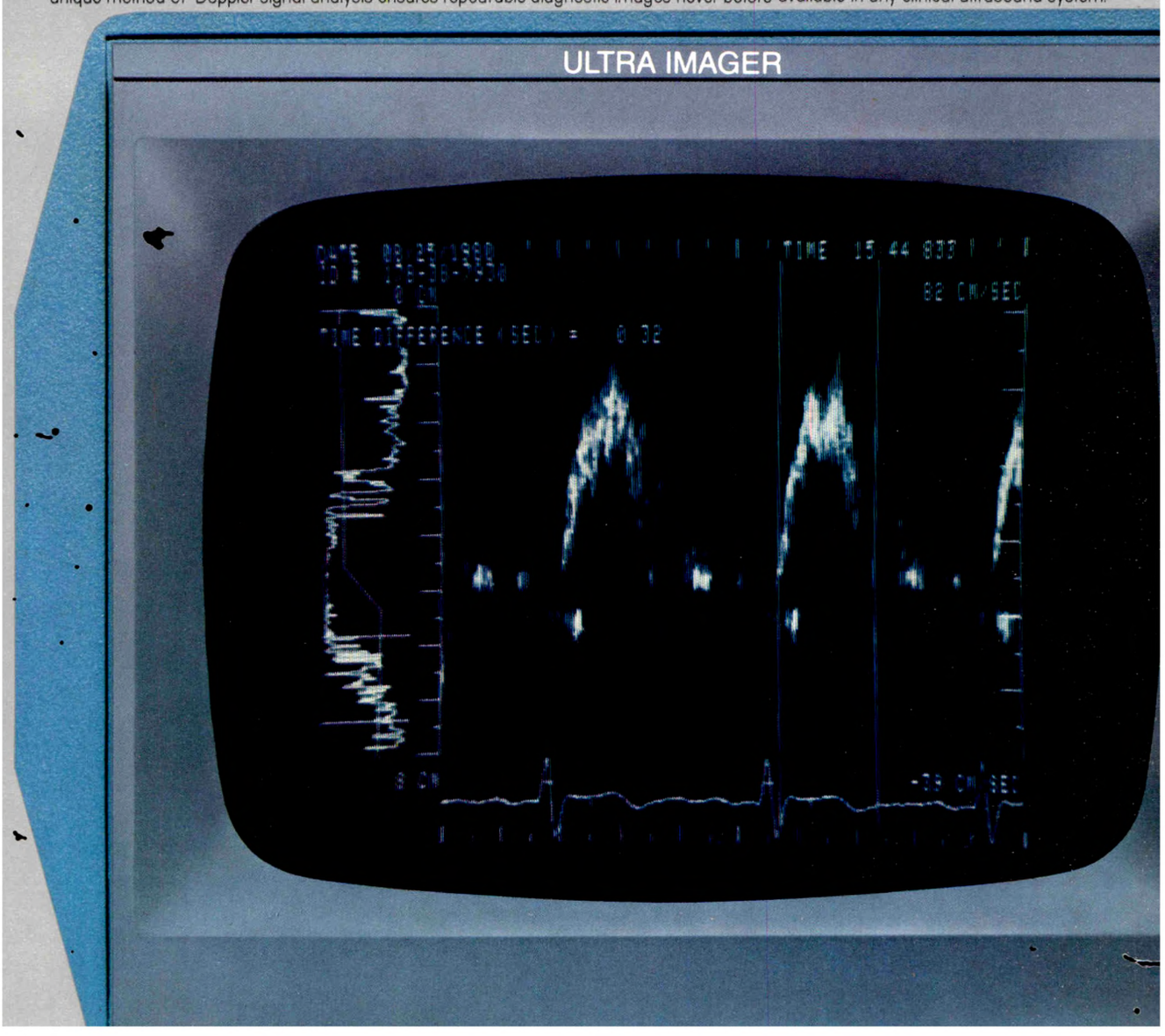

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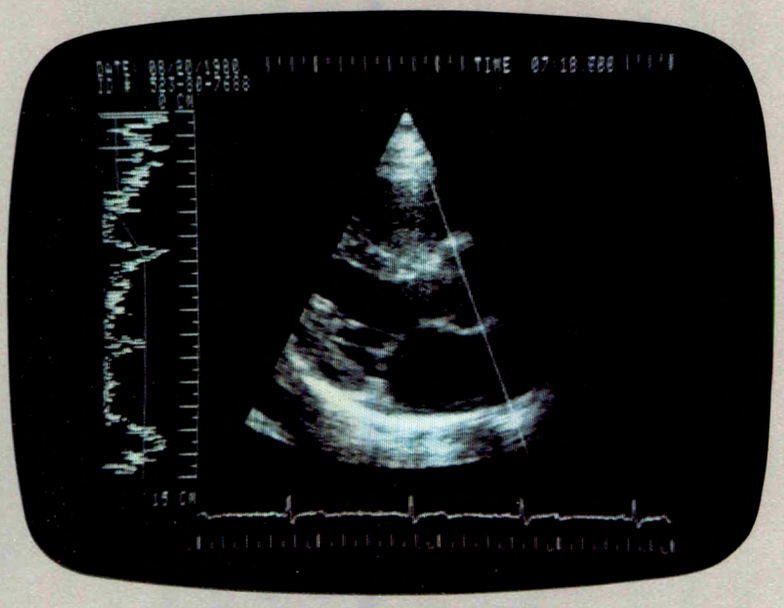

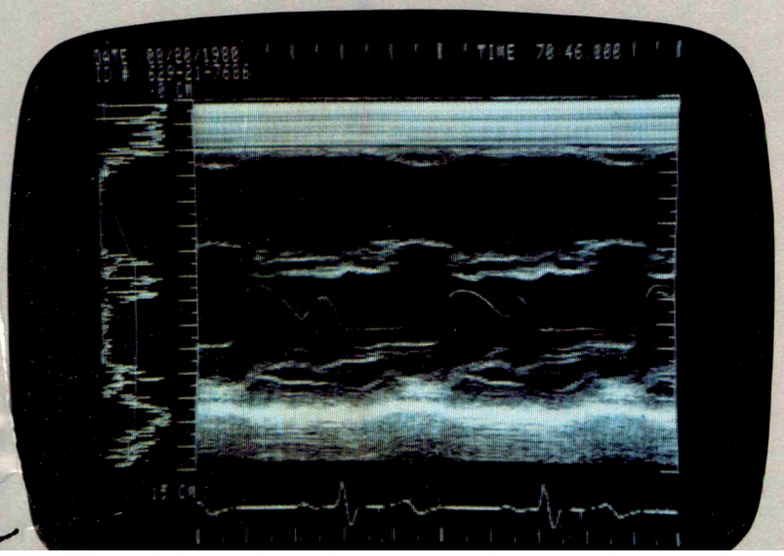

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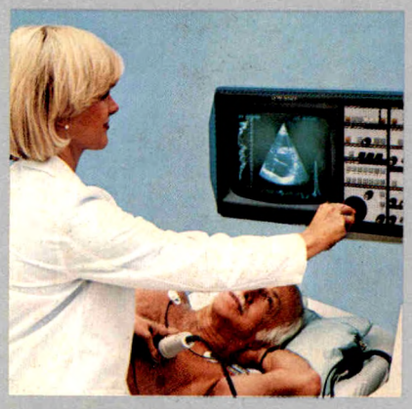
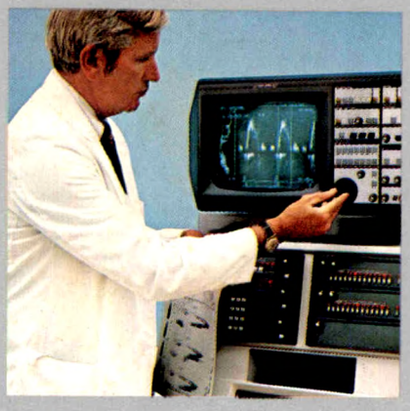


Operator can position the transducer and be within convenient reach of all necessary scan controls.



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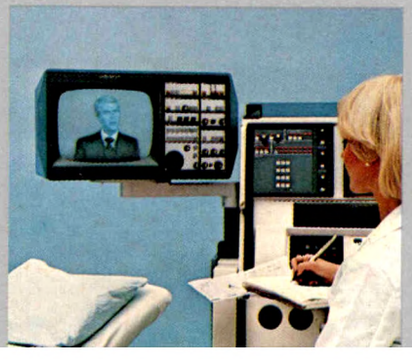

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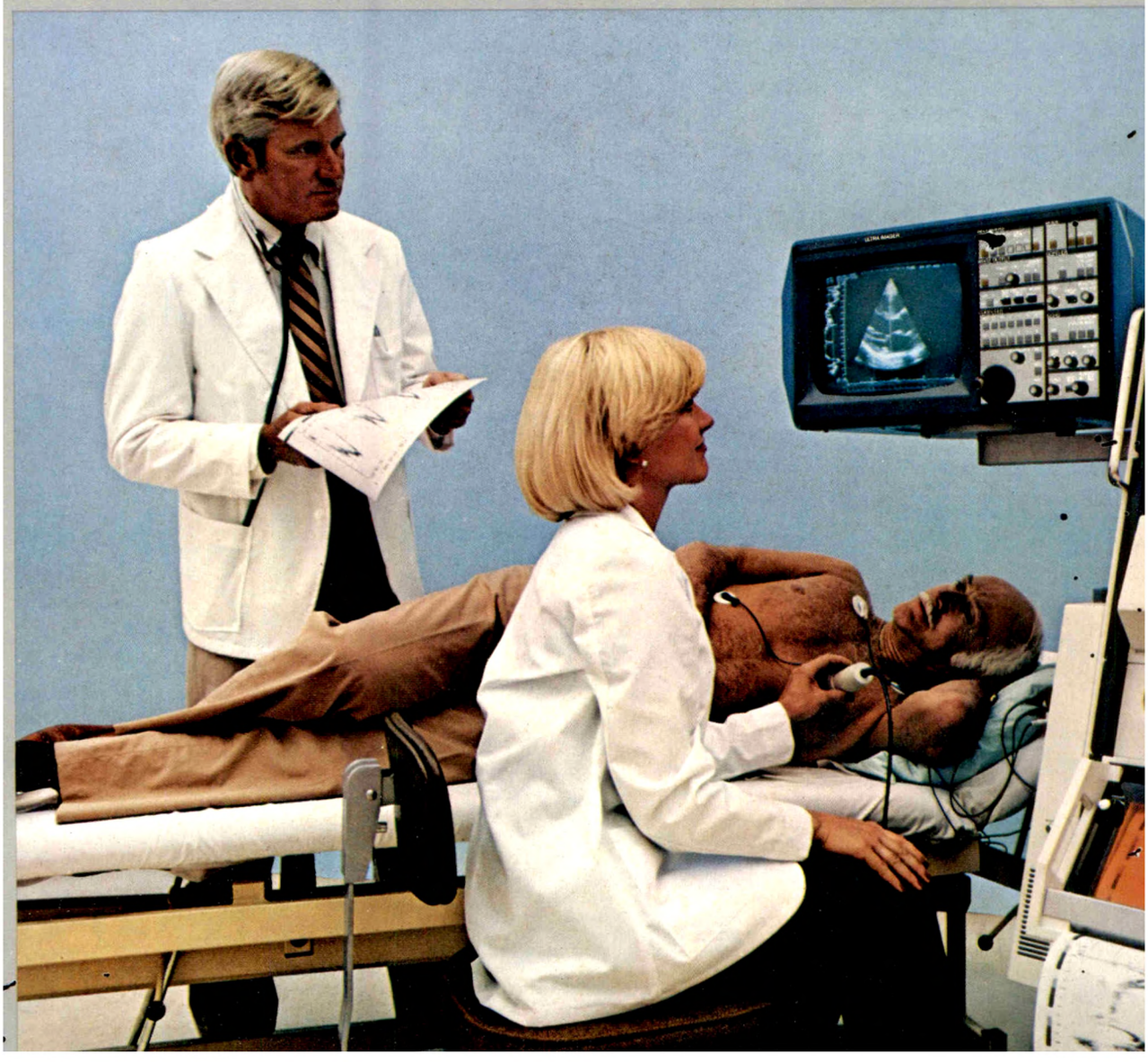

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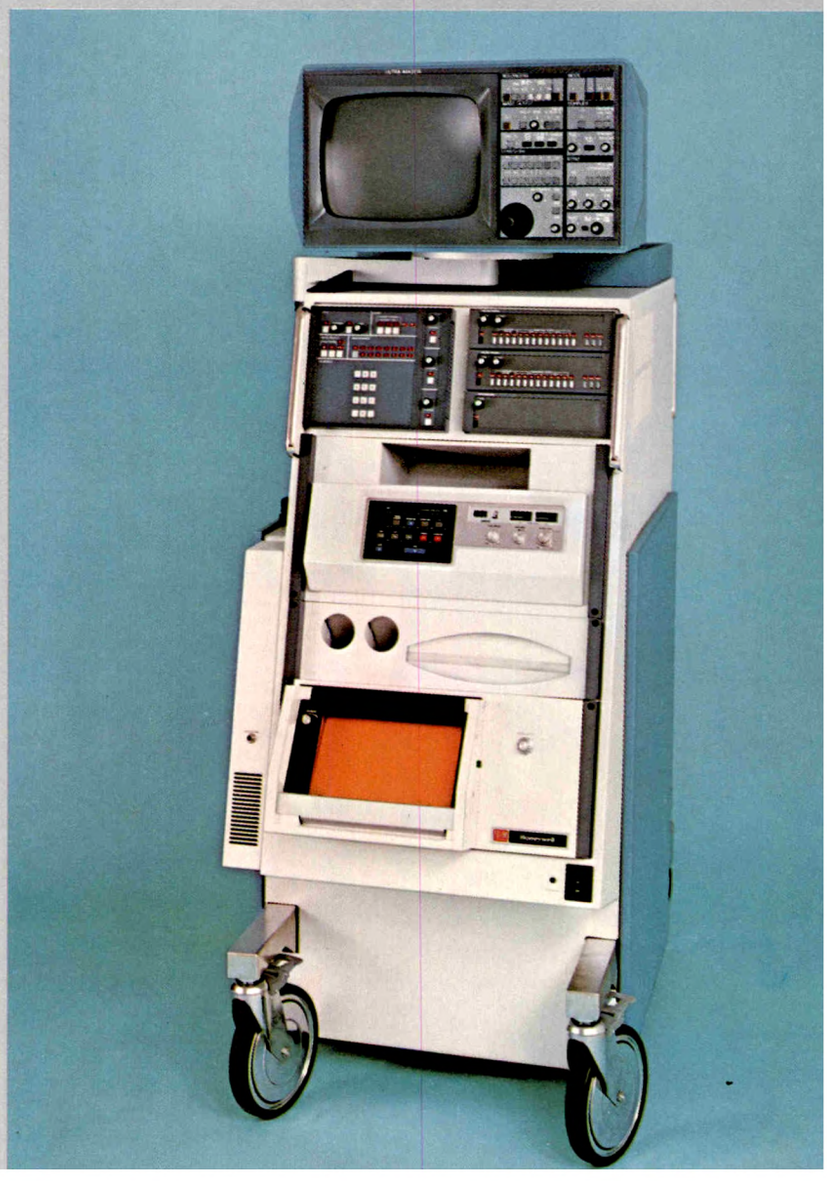

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Patients with obstructive coronary artery disease and stable, exertional angina respond to the alpha adrenergic stimulus of the cold pressor test with an inappropriate increase in coronary vascular resistance. The clinical significance of this abnormal response and its possible role in the pathogenesis of ischemic heart disease are discussed.

Comparison of the anti-anginal agents currently in use or undergoing investigation suggests that the calcium antagonists may be the most effective therapy for coronary vasoconstriction. Nifedipine, 10 mg buccally, successfully prevented the increase in coronary vascular resistance during the cold pressor test in 10 of 10 patients, whereas the response in placebo-treated patients was unaltered. This dose of nifedipine was without effect on systemic hemodynamics or myocardial oxygen consumption, suggesting a selective antivasoconstrictor effect on the coronary vasculature.

The rational therapy of ischemic heart disease is dependent on our understanding of the pathogenetic mechanisms that result in angina pectoris and myocardial infarction. The concept that myocardial perfusion is limited only by the fixed, obstructive lesions of coronary artery disease is now giving way to the growing recognition that abnormal coronary vasoconstriction can also, in some instances, restrict blood flow and contribute to myocardial ischemia.[1] The adverse effects of altered coronary tone have been most dramatically demonstrated as the coronary vasospasm of Prinzmetal's angina,[2,3] but similar mechanisms have also been implicated as a cause of angina at rest and myocardial infarction[7,8] in some patients. However, it is not necessary to invoke coronary vasoconstriction to account for the symptoms of the larger group of patients with obstructive coronary disease and stable, exertional angina.[9] A transient increase in myocardial oxygen demand, beyond the oxygen-delivering capabilities of the stenotic coronary arteries, is sufficient to cause ischemia in such patients. Nevertheless, a variety of evidence from recent investigations[10] suggests that even in these patients, coronary vasoconstriction can occur and, by restricting myocardial blood flow during periods of enhanced metabolic demand, contribute to the development of myocardial ischemia.

Before the implications of these concepts can be discussed, it is necessary to address three questions: (1) What is the evidence that coronary vasoconstriction occurs in patients with stable, exertional angina? (2) What is the clinical significance of coronary vasoconstriction? (3) What is the appropriate therapy for this disorder?

Demonstration of Coronary Vasoconstriction in Patients With Exertional Angina

The human coronary circulation is subject to metabolic, mechanical and neurogenic influences.[11] In patients with atherosclerotic heart disease, the presence of stenotic lesions in epicardial vessels imposes additional hemodynamic restraints on the vasodilatory response to metabolic stimuli.[12] The strong correlation of coronary blood flow and myocardial

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oxygen consumption[13] and the limited effects of sympathetic nerve stimulation on coronary tone in anesthetized animals[14] led to the earlier conclusion that coronary blood flow was predominantly controlled by locally released myocardial metabolites.[15] However, it has become apparent from more recent studies in conscious animals and man that alpha adrenergic vasoconstrictor mechanisms exert a significant influence on coronary vascular tone.[16–18] Reflex reduction in this alpha adrenergic tone during carotid sinus nerve stimulation results in coronary vasodilation[16]; conversely, alpha adrenergic activation during exercise and other physiologic stimuli cause coronary vasoconstriction despite increased myocardial metabolic demand.[19,20]

Effects of neurogenic stimulation by the cold pressor test: To evaluate the effects of neurogenic stimulation on the human coronary circulation, we have challenged patients with the cold pressor test, a stimulus that causes peripheral vasoconstriction mediated by alpha adrenergic receptors, while measuring coronary sinus blood flow by the thermodilution technique.[21] In subjects with normal coronary arteries, the cold pressor test produced an increase in mean arterial pressure, and a parallel increase in coronary sinus blood flow. Therefore, coronary vascular resistance remained unchanged (Fig. 1). In patients with coronary artery disease, however, the increase in blood pressure was not accompanied by an increase in coronary sinus flow. Coronary vascular resistance in these patients was significantly increased.

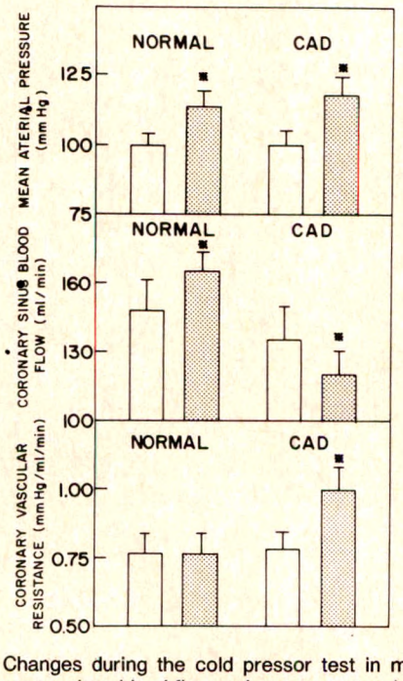


FIGURE 1. Changes during the cold pressor test in mean arterial pressure, coronary sinus blood flow and coronary vascular resistance in 12 normal subjects and 12 patients with coronary artery disease (CAD). **Open bars** = values at rest; **stippled bars** = values during cold pressor test. **Brackets** represent 1 standard deviation. (* = $p < 0.05$ compared with resting values for same group.)

The occurrence of coronary vasoconstriction during the cold pressor test appears to be a common feature of obstructive coronary artery disease and has been demonstrated in more than 60 patients studied in our laboratory. All of these patients had stable, exertional angina with no clinical symptoms or electrocardiographic evidence of Prinzmetal's angina.

Clinical Significance of Coronary Vasoconstriction

The demonstration of abnormal coronary vasoconstriction in patients with coronary artery disease would be of minor interest if the vasoconstriction caused no significant hemodynamic changes or symptoms. However, as shown in Table I, angina pectoris and other adverse effects occur during the cold pressor test in a sizable proportion of patients subjected to this stimulus.

Angina: Angina developed during the cold pressor test in approximately 30 percent of patients. Although 12 lead electrocardiograms were not routinely obtained, the chest pain was described by all patients as typical of that occurring during exertion, and subsided in each patient only after cessation of the cold pressor test. Of interest is the development of angina in these patients at a time when myocardial oxygen consumption, estimated by the heart rate-blood pressure product, became only slightly elevated, that is, by 10 to 20 percent. In the patients in this group who subsequently underwent rapid atrial pacing in the absence of the cold pressor test, the rate-pressure product could be elevated to much higher levels, that is, to 90 to 110 percent above the control level before angina developed.[22] These data suggest that the coronary vasoconstrictor response can effectively lower the "anginal threshold" by restricting myocardial blood flow.

Myocardial metabolism: Objective evidence of myocardial ischemia, as judged by a conversion of the arterial-coronary sinus lactate difference from positive to negative,[23] that is, lactate production, was demonstrated during the cold pressor test in 4 of 15 patients in whom these measurements were made. A less dramatic indication of impaired myocardial perfusion, that is, widening of the arterial-coronary sinus oxygen dif-

TABLE I

Incidence of Adverse Effects of Coronary Vasoconstriction During the Cold Pressor Test

Event	Patients Affected	
	n	%
Angina	12 of 39	31
Negative myocardial lactate uptake	4 of 15	27
Widened arterial-coronary sinus oxygen difference	14 of 15	93
New abnormalities in regional myocardial blood flow	9 of 10	90
Global decrease in left ventricular ejection fraction	10 of 10	100

ference (from 11.5 ± 0.3 to 12.3 ± 0.3 ml/100 ml, $p < 0.05$[24]), was observed in 14 of the 15 patients. Because the coronary sinus catheter samples blood from multiple areas of left ventricular myocardium, it is possible that greater changes in oxygen extraction occurred in some regions, but were masked by normally oxygenated venous blood from well perfused regions.

Regional myocardial blood flow: Preliminary studies measuring regional myocardial flow during the cold pressor test by the xenon-^{133} washout technique[25] have yielded two important results: (1) The abnormal increase in coronary vascular resistance measured by thermodilution in patients with coronary artery disease has been confirmed by an entirely independent method of quantifying myocardial blood flow; and (2) in patients with coronary disease, blood flow was unchanged, or actually decreased, only in those regions of myocardium supplied by diseased coronary arteries; blood flow to regions supplied by normal vessels increased appropriately, as it did in all regions in normal subjects. Abnormal coronary vasoconstriction, therefore, appears to occur only in the distribution of diseased vessels and is not a generalized vascular disorder.

Left ventricular function: Radionuclide ventriculography was used to assess noninvasively changes in left ventricular function during the cold pressor test in 10 patients. Global ventricular function (left ventricular ejection fraction) decreased slightly, but significantly (5 to 10 percent) in all patients. A new abnormality of segmental wall motion could be identified in only one patient. It is not yet known whether the decrease in ejection fraction is specifically the result of coronary vasoconstriction or the result of increased afterload, or of both mechanisms.

Coronary vasoconstriction during exercise: Although our studies have used the cold pressor test as a provocative stimulus to demonstrate coronary vasoconstriction in patients with coronary artery disease, it is possible that adrenergic stimulation during other forms of stress, such as exercise, may also activate neurogenically mediated vasoconstriction.[19,20] Frank spasm of epicardial arteries during exercise has been documented by coronary arteriography in some patients with exertional angina.[26] More subtle forms of vasoconstriction, detectable only by direct measurements of coronary blood flow, may be more common. The presence of even normal alpha adrenergic tone in the coronary circulation during exercise could be deleterious in patients whose vasodilatory reserve is already diminished by obstructive coronary lesions. Further studies are clearly needed to clarify the role of coronary vasoconstriction in the pathogenesis of exercise-induced ischemia.

Therapy of Coronary Vasoconstriction

The recognition of a vasoconstrictive component in various forms of ischemic heart disease has renewed interest in alternative forms of therapy for this disorder. It is appropriate to review our experience with representative agents from each of these groups in relation to coronary vasoconstriction.

Propranolol: The beta adrenergic blocking agent propranolol is obviously effective in the treatment of myocardial ischemia due to transiently increased myocardial oxygen demand. It appears to be considerably less useful in the treatment of vasospastic (Prinzmetal's) angina.[27,28] Propranolol can secondarily increase coronary vascular resistance by reducing myocardial oxygen consumption[29] and, theoretically, by inhibiting vasodilatory mechanisms mediated by $beta_2$ receptors, could potentiate the coronary response to vasoconstrictor stimuli.[30] Studies reporting a worsening of symptoms in some patients with variant angina during propranolol therapy support such a hypothesis.[31,32]

To assess the effects of propranolol on the abnormal coronary vasoconstriction of patients with coronary artery disease, we compared the cold pressor test responses of patients receiving their usual doses of propranolol during the test to those of a similar group of patients who had discontinued propranolol therapy at least 8 hours before catheterization[22] (Table II). There were no significant differences in the hemodynamic or coronary vascular responses of the two groups. The patients with normal coronary arteries had a normal response; the patients with coronary artery disease had an abnormal vasoconstrictor response. These data indicate that the vasoconstrictor response is not an artifact caused by beta adrenergic blockade, but they also suggest that vasoconstriction is not prevented by propranolol. Sequential cold pressor tests in the same patient, before and after acute administration of propranolol, will be needed to confirm the latter suggestion.

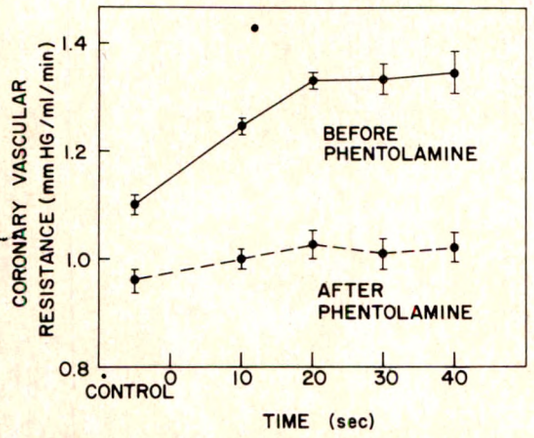
Nitroglycerin and long-acting nitrates: Nitrates, of course, are potent vasodilators, and administration of sublingual or intravenous nitroglycerin is effective in preventing or relieving coronary vasospasm. The prophylactic effectiveness of long-acting nitrates is less certain. Less than half of a large series of patients with Prinzmetal's angina manifested even partial improvement with long-acting nitrate therapy.[28] Maseri et al.[8] reported that 37 of 87 consecutive patients admitted with vasospastic angina had an acute myocardial infarction within 1 month despite treatment with large

TABLE II

Cold Pressor Test Responses With (+) and Without (−) Propranolol

	ΔBP	ΔCSBF	ΔCVR
Normal subjects			
+ propranolol (n = 12)	+14 ± 1%	+15 ± 4%	0 ± 2%
− propranolol (n = 14)	+17 ± 2%	+26 ± 3%	−3 ± 1%
Patients with CAD			
+ propranolol (n = 12)	+18 ± 3%	−10 ± 3%	+27 ± 3%
− propranolol (n = 13)	+20 ± 2%	−5 ± 1%	+25 ± 3%

Values expressed as mean values ± standard error of the mean.
CAD = coronary artery disease; ΔBP = % change in mean arterial pressure during the cold pressor test; ΔCSBF = % change in coronary sinus blood flow; ΔCVR = % change in coronary vascular resistance.



IGURE 2. Effect of 5 mg of intravenous phentolamine on the change ı coronary vascular resistance during the cold pressor test in three atients with coronary artery disease. Values represent mean ± tandard error of the mean. (After Mudge et al.[21])

loses of nitrates. The coronary vasoconstrictor response o the cold pressor test likewise appears to be unaffected y long-acting nitrates. The responses in patients naintained on nitrate therapy were, as in the case of ropranolol, indistinguishable from those in whom nirate therapy had been withdrawn. These findings may e explained by the relative specificity of clinically seful doses of orally administered nitrates for venous apacitance vessels rather than arterial resistance vesels.[33] Unfavorable pharmacokinetics of oral nitrates ıay also play a role, since a recent report[34] suggests that ntinuous intravenous infusion of nitrates may be ective in preventing coronary vasospasm. Such therapy obviously impractical for patients with chronic, stable ngina.

Alpha adrenergic antagonists (phentolamine): he third group of agents, the alpha adrenergic antagnists, should theoretically be effective in preventing he abnormal coronary vasoconstrictor response because he cold pressor test is at least partly mediated by acivation of alpha adrenergic vascular receptors. Coroary vasoconstriction during the cold pressor test *can* e blocked by intravenous phentolamine (Fig. 2); owever, the effect is nonspecific because the systemic ressor response is also blocked. This lack of specificity nderlies the difficulties in the clinical use of an alpha drenergic antagonist. It is difficult to maintain adeuate alpha adrenergic blockade in ambulatory patients ithout adverse effects, such as postural hypotension. n patients also receiving larger doses of a beta adrenrgic antagonist, the result is comparable to chemical ympathectomy and not well tolerated.

Calcium antagonists (nifedipine): The final group f agents, the calcium antagonists, is composed of sevral vasodilator drugs with an apparently unique ıechanism of action. Unlike nitrates and other vasoilators, they can prevent smooth muscle contraction y inhibiting the slow inward current of calcium during

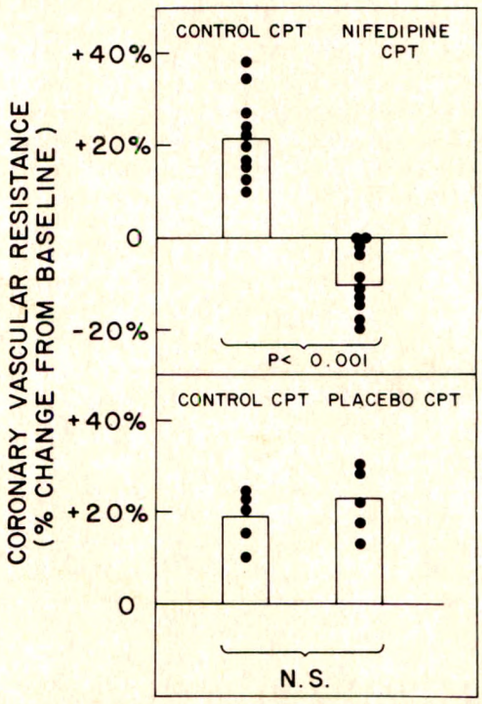


FIGURE 3. Changes in coronary vascular resistance during a cold pressor test (CPT) in 10 patients before and after administration of nifedipine (**upper panel**) and in 5 patients before and after placebo (**lower panel**).

depolarization that is responsible for excitation-contraction coupling.[35] Although used for several years in Europe and Japan in the treatment of classic exertional angina,[36] they have recently become of great interest because of their antispasmodic properties.[37]

The favorable experience with one of these drugs, nifedipine, in preventing the vasospasm of Prinzmetal's angina,[27,28] prompted us to investigate its usefulness in preventing the coronary vasoconstrictor response of patients with coronary artery disease and exertional angina. Fifteen patients underwent a cold pressor before and after the administration of nifedipine (10 mg buccal) or placebo.[24] Figure 3 illustrates that nifedipine

TABLE III

Hemodynamic Values During Control Study and Nifedipine Cold Pressor Tests

	MAP (mm Hg)	LVEDP (mm Hg)	$M\dot{V}O_2$ (ml/min)
Before nifedipine			
Baseline	102 ± 4	13 ± 3	15.8 ± 1.1
Cold pressor test	120 ± 5	18 ± 3	16.8 ± 1.4
After nifedipine			
Baseline	99 ± 3	12 ± 2	14.7 ± 1.4
Cold pressor test	113 ± 3	17 ± 3	17.9 ± 1.5

Values expressed as mean values ± standard error of the mean.
LVEDP = left ventricular end-diastolic pressure; MAP = mean arterial pressure; $M\dot{V}O_2$ = myocardial oxygen consumption.

successfully prevented coronary vasoconstriction in each of the 10 patients tested, while the response in the 5 patients given placebo was essentially unchanged. Four of the patients who subsequently received nifedipine had angina during the control cold pressor test; none of these patients were symptomatic during the nifedipine cold pressor test. Nifedipine, at the dose used, prevented abnormal coronary vasoconstriction without affecting systemic hemodynamics, either at rest or during the cold pressor test (Table III). Because the changes in arterial pressure, left ventricular end-diastolic pressure and myocardial oxygen consumption were comparable during the two cold pressor tests, nifedipine appeared to exert a selective, antivasoconstrictor effect on the coronary circulation. At this dosage, nifedipine was well tolerated without side effects by all patients.

Conclusions

Coronary vasoconstriction has been demonstrated in many types of ischemic heart disease. Coronary arterial vasospasm plays a pathogenetic role in Prinzmetal's angina, and probably in some forms of unstable angina and myocardial infarction as well. Milder, but clinically significant degrees of coronary vasoconstriction occur in patients with stable, exertional angina during the stimulus of the cold pressor test. Studies in experimental animals and in patients with coronary artery disease indicate that such vasoconstrictor mechanisms can effectively restrict coronary blood flow when myocardial demand is increased, and thus may play a contributory role in the development of ischemia. Of the anti-anginal drugs, calcium antagonists appear to be the most effective in preventing coronary vasoconstriction.

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Nifedipine in the Treatment of Unstable Angina, Coronary Spasm and Myocardial Ischemia

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The effects of nifedipine, a potent calcium antagonist, were studied in patients with unstable angina, coronary spasm and myocardial ischemia. Data from two separate groups of patients studied in the cardiac catheterization laboratory indicate that intracoronary injection of nifedipine promptly reversed coronary spasm—whether provoked or spontaneous—in five of six patients. In other patients, direct intracoronary injection of the drug was compared with intravenous administration. After intracoronary injection, local mechanical cardiac action virtually ceased, and the ventricular wall became thinner during systole. Thus, a specific inhibitory action on contractile energy expenditure could be demonstrated in the presence of increased coronary flow. This "oxygen-sparing" effect was tested in a group of 31 patients with symptomatic unstable angina whose pain at rest, with ST-T changes, had not responded to 8 hours of treatment with maximal beta adrenergic blockade, nitrates and bed rest. The addition of 6 × 10 mg of nifedipine rendered 27 of these patients asymptomatic within 1.5 hours. In the four patients who did not respond, coronary arteriography demonstrated severely stenotic lesions. Two of the four patients subsequently responded to intraaortic balloon pumping and bypass surgery; one patient had a myocardial infarction and one who had a 90 percent reduction in the diameter of the left main coronary artery, died.

It is concluded that nifedipine should be added to beta adrenergic blockade therapy if the latter does not appear to be immediately effective. This combination has not been shown to cause any hemodynamic deterioration, and only a minority of the patients treated sustained a myocardial infarction during the first 3 months of follow-up. The use of nifedipine in unstable angina deserves further clinical evaluation.

The concept that coronary vasospasm is one cause of angina pectoris and myocardial infarction has recently been rediscovered, almost a century after the original descriptions by Latham.[1] In fact, in the past few years, several investigators[2–7] have brought about a shift in attitude concerning the pathophysiologic derangements underlying myocardial infarction. It is now accepted that temporary obliteration of coronary blood flow due to increased vessel wall tone, even in the absence of fixed coronary arterial obstruction and stenosis, can lead to myocardial infarction. Most likely, intermittent and fixed coronary stenosis act in combination; that is, increased vasomotility of a major vessel around a fixed obstruction causes the critical reduction in flow that leads to irreversible ischemia. To what extent platelet aggregates and disturbances in prostaglandin metabolism play a role is as yet unclear, but their effects may well be additive.

Such a view opens new avenues for treatment because, if coronary spasm or increased vascular tone can be recognized, timely relief of the condition should reverse the process of impending infarction. Our cur-

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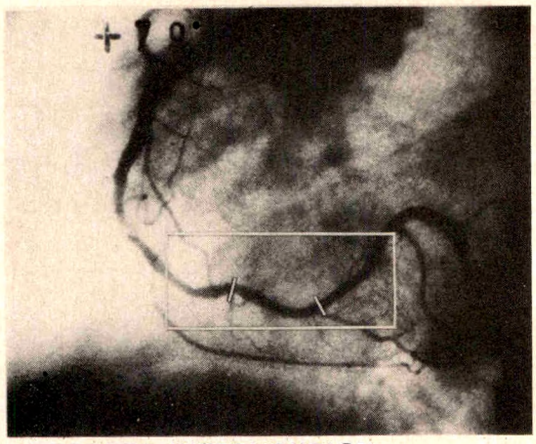

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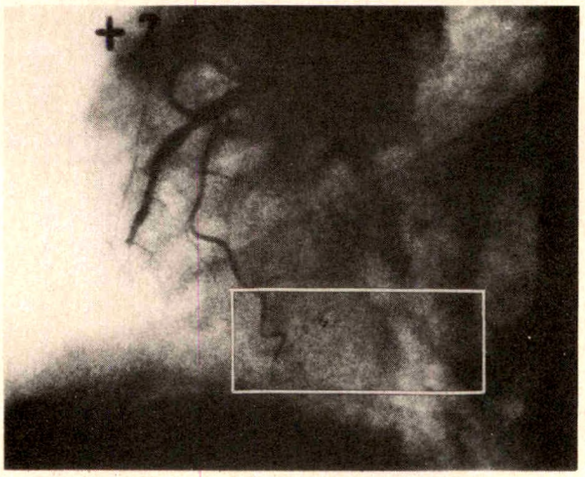

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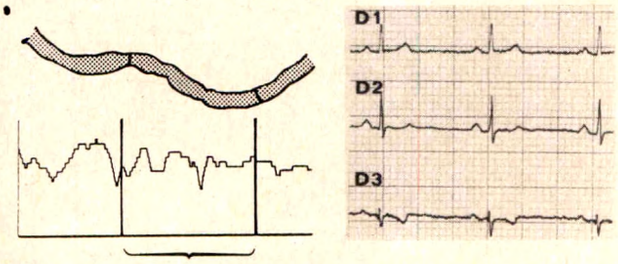

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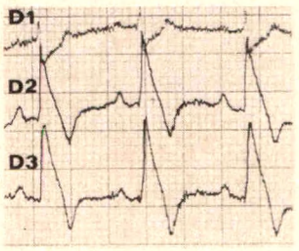

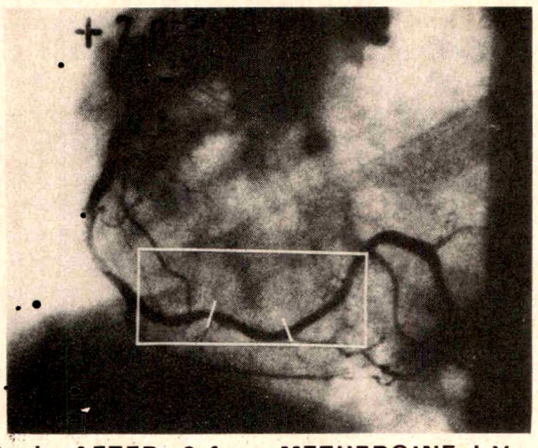

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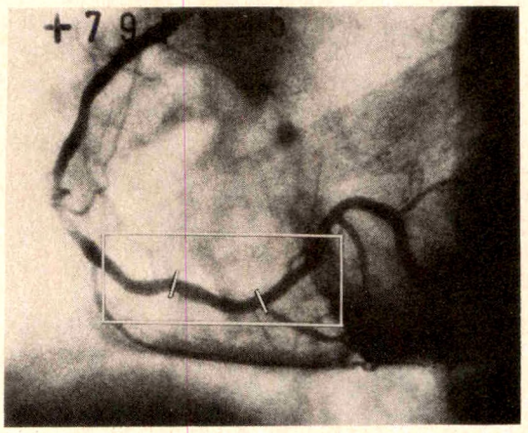
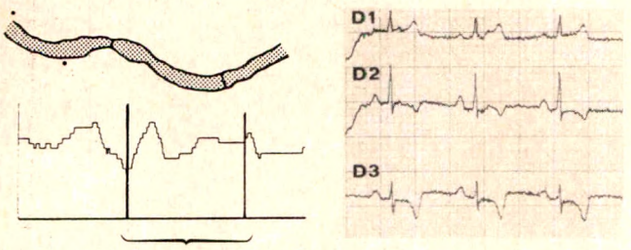
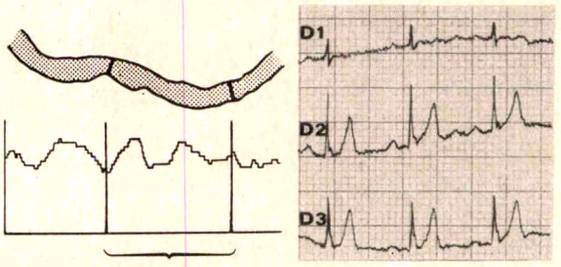


1 min AFTER 0.2 mg NIFEDIPINE I.C.



mean diameter 14.8 units



mean diameter 21.5 units

FIGURE 1. Patient I (Table I). Four frames from a cineangiogram. **Upper left,** the involved right coronary artery before intervention. **Lower left and upper right** spasm provoked by an intravenous (I.V.) injection of methergine (ergonovine). Note that in **the upper right frame** the artery has virtually "disappeared". **Lower right,** abolition of the spasm by intracoronary (I.C.), injection of nifedipine. Simultaneously recorded electrocardiograms (leads I, II and III) are shown. An automated measurement system was employed to grade changes in the caliber of the right coronary artery (**bottom**) which is expressed in units reflecting a surface area.[16]

rent study relates to several experiences that provide a partial answer to the potential efficacy of nifedipine in this scheme of events. First, nifedipine's powerful action as a calcium antagonist leads to vessel dilation, which has proved effective in classic Prinzmetal's angina in which spasm is known to be the main causative mechanism. Direct intracoronary injection of nifedipine has been observed to lead to prompt restoration of the normal caliber of a totally occluded vessel.

However, other actions of nifedipine may make this drug equally attractive for the treatment of patients with unstable angina pectoris. In our laboratory, measurements of left ventricular function, both in pigs and in human subjects, have shown that local mechanical contraction ceases for up to 5 minutes when nifedipine is injected into the coronary artery supplying the ischemic cardiac muscle. In patients with unstable angina, the best protective action for ischemic cells might be provided if coronary flow could be increased and local consumption of oxygen simultaneously decreased, while electrical activation continued normally.

To test these hypotheses, we studied a group of patients admitted to the coronary care unit with angina pectoris at rest and transient S-T segment or T wave changes but without evidence of acute myocardial infarction, such as abnormal enzyme release and development of Q waves. At our center, this high risk group of patients with unstable angina is routinely managed with bed rest and administration of oxygen, sedatives, long-acting nitrates and beta adrenergic blocking agents. The therapeutic objective is to return the patient with signs of myocardial ischemia to a stable and asymptomatic state, thereby preventing infarction. In our hands, this regimen has not proved successful in all patients. In fact, until recently it was our policy to proceed to emergency coronary bypass surgery (in several cases with prior intraaortic balloon pumping) when no relief was obtained after 8 to 12 hours of maximal therapy with beta adrenergic blocking agents.[8]

Methods

Study 1

The methodology employed for the animal data quoted under Results has been published elsewhere and will not be repeated here.

For the first part of the clinical study, data were collected from 6 patients who underwent cardiac catheterization because of myocardial ischemia suspected to be secondary to spasm and from 10 other patients who have had bypass surgery 1 year before catheterization. In the latter group, a total of 26 pairs of radiopaque platinum markers had been implanted on the epicardium at operation. Seventeen of these marker pairs (in 10 patients) were placed on areas newly supplied by blood from the coronary arterial bypass graft, and nine pairs of markers (in 9 patients) were placed in areas not supplied by the coronary arterial system.

Patients with coronary spasm: Of the six patients with suspected coronary arterial spasm, two showed the full-fledged clinical syndrome of Prinzmetal's angina. During catheterization, spontaneous spasm was observed in three of the six, and in another two spasm was induced by intravenous injection of methergine (an ergot alkaloid similar to ergonovine). In the sixth patient, spasm was induced during manipulation of the catheter. In each patient, as soon as spasm was observed, the average dose of nifedipine (2 μg/kg body weight) was selectively injected into the coronary artery in spasm and biplane filming was performed (Fig. 1, Table I). This average dose had been selected as a result of previous studies in our laboratory.[9] No effort was made to test the patient's response to nitrates before administration of nifedipine.

Patients after coronary bypass surgery: During recatheterization of 10 postoperative patients a pacing catheter was placed into the right atrium (Fig. 2). Heart rate was fixed at 10 beats above the spontaneous rate present before the pharmacologic intervention. Left ventricular pressures were recorded with a double micromanometer (Millar PC770 or 780). The methodology for measuring regional shortening from epicardial radiopaque markers has been described in detail elsewhere.[10] In brief, the radiopaque marker pairs implanted in the epicardium at operation are filmed during synchronized biplane cinefluoroscopy at 50 frames/s. The absolute distances between each marker pair are calculated, with five consecutive heart beats being analyzed as a control set before intrabypass injection of nifedipine and again 30, 60, 120 and 180 seconds after the injection. During this period, variables derived from left ventricular pressure measurements are monitored continuously by means of the beat to beat analysis program of our cardiac catheterization laboratory computer.[11] Pressures were recorded for a period of 5 minutes before and during the injection of nifedipine. End-diastolic pressure, peak systolic pressure, peak positive first derivative of left ventricular pressure (dP/dt), cycle length, peak velocity of contractile elements (V_{ce}) and maximal velocity of contractile elements (V_{max}) were derived by means of the on-line computer program. In addition, an analysis of the isovolumic relaxation phase was carried out by calculating the peak negative dP/dt. The relaxation time constant was determined by a least-squares fit of a monoexponential equation describing the fall of left ventricular pressure from the moment

TABLE I

Arteriographic Findings and Effect of Nifedipine in Six Patients With Either Spontaneous or Induced Coronary Arterial Spasm

Case	Spasm	Arteriographic Findings (vessel and % obstruction)	Intracoronary Nifedipine*	Intravenous Nitroglycerin*
1	Methergine-induced	RCA (100%)	+	...
2	Methergine-induced	LCx (100%)	−	+
3	Spontaneous	RCA (75%)	+	...
4	Spontaneous	LAD (75%)	+	...
5	Catheter-induced	RCA (75%)	+	...
6	Spontaneous	LCx (100%)	+	...

* Immediate administration of intracoronary nifedipine relieved the obstruction completely in five of six patients; intravenous nitroglycerin proved effective in one.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; + = effective; − = not effective; ... = not administered.

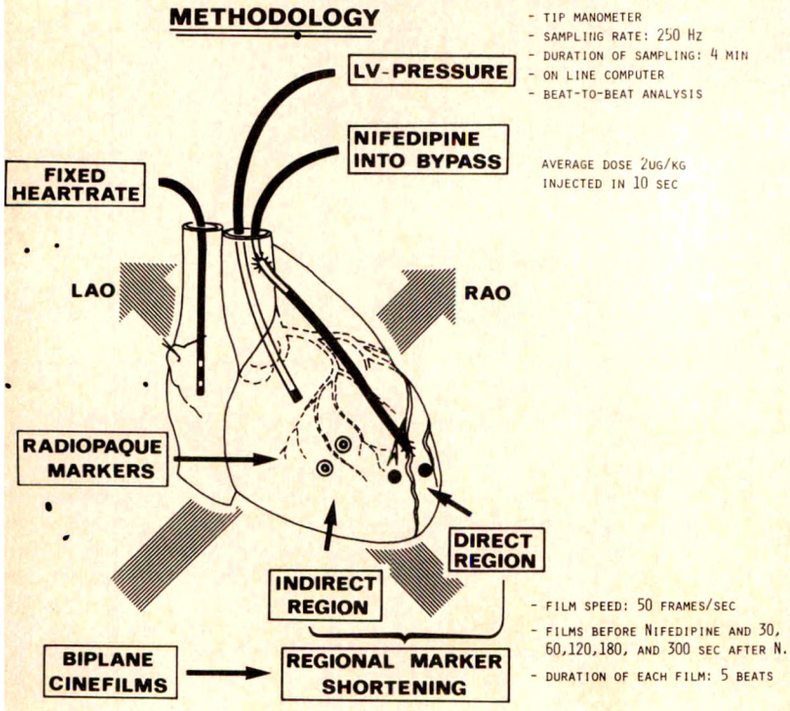


FIGURE 2. Diagram of the principal methods employed in the study. See text and Reference 10 for details on the measurement of regional shortening with radiopaque markers attached to the epicardium during coronary bypass surgery. LAO = left anterior oblique; LV = left ventricular; N. = nifedipine; RAO = right anterior oblique.

of peak negative dP/dt to that existing at a pressure of 35 mm Hg (Fig. 3).

Study 2

Patients with unstable angina: The second part of the study, was carried out between June 1, 1979 and January 1, 1980, when 720 patients with various symptoms of coronary artery disease were admitted to our coronary care unit. Forty-seven of these patients had precordial pain at rest that was typical of angina pectoris and that persisted or worsened. In all 47 patients, transient ST-T changes but no new Q wave formation were documented in the coronary care unit during angina at rest. The patients' serum enzyme levels were often elevated but in no instance reached values twice the normal in our laboratory.

On admission, all patients were placed in a private room, although they remained directly accessible to the nursing staff. Hemodynamic monitoring was initiated immediately by means of a Swan-Ganz thermodilution catheter advanced from the subclavian or right jugular vein or an arm vein into the pulmonary artery. If either hypotension or hypertension was present initially, a catheter was inserted into the left radial artery with use of local anesthesia. All patients received heparin intravenously (30,000 units or less every 24 hours). A semiautomated monitoring system facilitated continuous recording of heart rate, cardiac rhythm and pul-

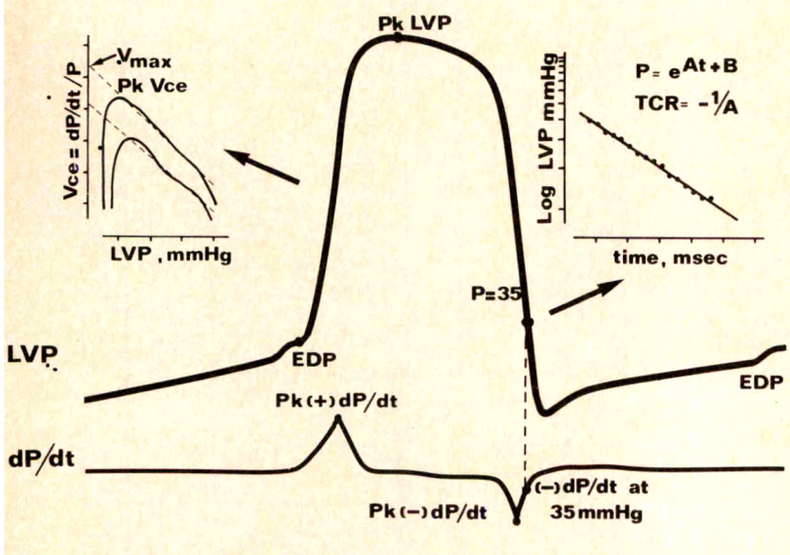


FIGURE 3. Isovolumic variables, as determined by the beat to beat analysis program of the catheterization laboratory computer system. dP/dt = rate of rise of left ventricular pressure; EDP = end-diastolic pressure; LVP = left ventricular pressure; P = 35 = pressure at 35 mm Hg; $P = e^{AT + B}$ = the constant and intercept of the regression line; Pk = peak; TCR = time constant for relaxation determined by slope (A) of pressure on log-linear plot; V_{ce} = velocity of contractile elements; V_{max} = maximal velocity of contractile elements.

monary arterial pressure, while systemic blood pressure and cardiac output were determined at regular intervals. During and after every attack of pain, a 12 lead electrocardiogram was recorded, and if pain persisted, the recording was repeated at 15 minute intervals. On admission and 6 hours after each attack of pain, creatine kinase, MB-creatine kinase and α-HBDH cardiac enzymes were measured.

After initial sedation, usually with oral diazepam (5 to 10 mg three times daily), the patient was given isosorbide dinitrate, 5 mg every 2 hours sublingually or, if necessary, intravenously. In addition, propranolol was administered intravenously at doses ranging from 1 to 10 mg until a heart rate of 60 beats/min was reached. Thereafter, propranolol was given orally at doses ranging from 400 to 800 mg every 24 hours. When propranolol was contraindicated, as in patients with lung disease, a cardioselective beta adrenergic blocking agent was chosen.

The 47 patients studied included 38 men and 9 women aged 29 to 77 years (mean 58). Three subgroups of patients could be identified: Twelve (group I) had no history of previous coronary artery disease, 25 (group II) had a history of long-standing coronary artery disease and the remaining 10 (group III) had a return of angina at rest within 2 weeks after discharge from the hospital where they had been treated for an acute myocardial infarction. Two patients in group II and one in group III had previously had coronary bypass grafting.

Results

Nifedipine injection into coronary bypass graft: Data collected from the patients studied during cardiac catheterization are shown in Tables I and II and Figures 4 and 5.[12] After direct injection of nifedipine into the coronary graft bypass the expected reduction in peak left ventricular systolic pressure occurred. There was also an increase in end-diastolic pressure as well as a marked decrease in peak positive dP/dt, peak negative dP/dt and V_{max}, and an increase in the relaxation time constant. All of these differences were statistically significant when compared with control measurements.

TABLE II

Pressure-Derived Variables After Intracoronary Bypass Injection of Nifedipine (10 injections, mean ± standard error of the mean)

	Control Value	Peak Effect
Peak LVP (mm Hg)	141 ± 8	124 ± 7*
EDP (mm Hg)	16 ± 2	26 ± 3*
Peak positive dP/dt (mm Hg/s)	1855 ± 118	1521 ± 73†
V_{max}(lengths/s)	55 ± 3	43 ± 2*
Peak negative dP/dt (mm Hg/s)	2133 ± 135	1575 ± 86*
Negative dP/dt at 35 mm Hg (mm Hg/s)	873 ± 43	598 ± 53†
Relaxation time constant (lengths/s)	39 ± 2	54 ± 3*

* $p < 10^{-5}$. † $p < 10^{-4}$.
dP/dt = rate of change of left ventricular pressure; EDP = end-diastolic pressure; LVP = left ventricular pressure; V_{max} = maximal velocity of contractile elements.

The shortening fraction during ejection, that is, the systolic phase of the cardiac cycle, was markedly decreased in the area directly perfused by the artery into which nifedipine had been injected (Fig. 4 and 5); in contrast, no changes were observed elsewhere in the heart. The onset of regional shortening was delayed and the shortening rate was diminished. Minimal length was shifted from end-systole to early diastole, as if contraction had continued during diastole.

These responses were previously observed in experimental animals in which regional wall thickness and blood flow in the left anterior descending coronary artery were measured in areas perfused by this artery after nifedipine was injected directly into it (Fig. 6A).[9] The difference between coronary arterial and pulmonary arterial infusion is shown in Figure 6. All changes in left ventricular variables were transient, and function returned to control levels within 5 minutes. All measurements were made at a constant rate of pacing, and direct slowing of contraction and relaxation must be inferred.

Oral nifedipine in unstable angina (Fig. 7): Sixteen of the 47 patients with unstable angina who were treated with propranolol or other beta blocking agents

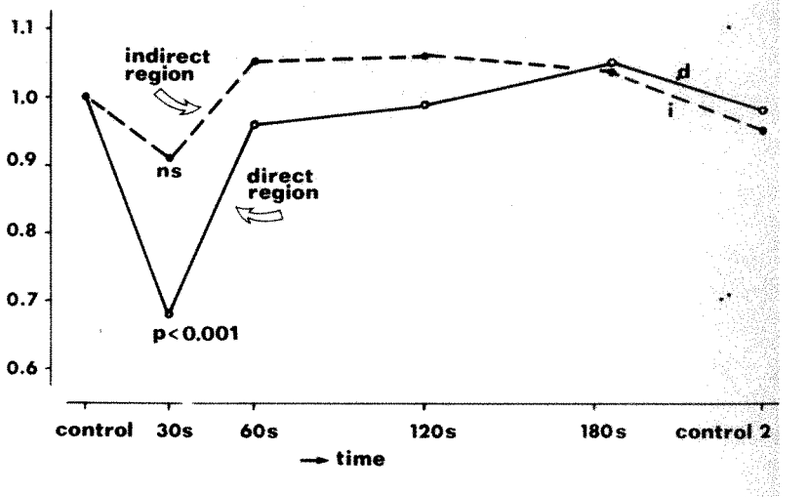


FIGURE 4. Normalized shortening fraction during ejection in selective regions as determined by movement of radiopaque markers (direct [d], n = 17) and independently perfused marker pair regions (indirect [i], n = 9). Values shown are relative changes from control values. Within 30 seconds of injection of nifedipine into the bypass graft a large and significant decline in the regional ejection fraction of the myocardium perfused by the bypass graft occurred (direct region) and recovery occurred rapidly; this was accompanied by only a small reduction in the localized ejection fraction of the myocardium not perfused by the graft.

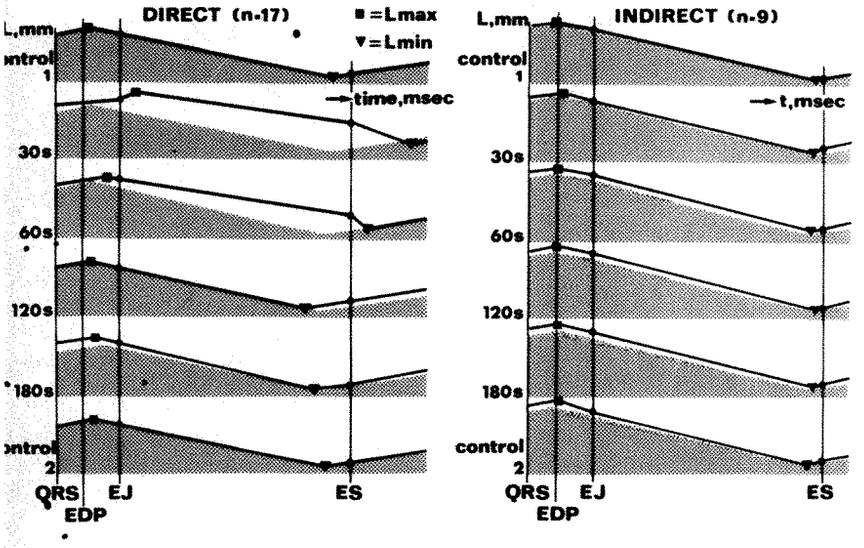


FIGURE 5. Regional shortening measured with pairs of radiopaque markers in (**left**) region of myocardium into which nifedipine had been injected (direct, n = 17) and (**right**) other regions of myocardium (indirect, n = 9). **From top to bottom:** Control period and 30, 60, 120, and 180 seconds after intrabypass injection of nifedipine. The **shaded area** represents the shortening pattern of the first control period. In selectively injected regions, the onset of regional shortening (L_{max}) is delayed, the shortening rate is diminished, and L_{min} is shifted from end-systole to early diastole. EDP = end-diastolic pressure; EJ = ejection; ES = end-systole. Left panel reproduced from Serruys et al.[12] by permission of the American Heart Association, Inc.

nd nitrates became asymptomatic 3 to 8 hours after the nset of treatment. Of the other 31 patients who, in ddition, received oral nifedipine in doses of 10 mg six mes a day, 27 became asymptomatic within 1.5 hours nd remained so for the remainder of their hospital stay; patients did not respond to nifedipine. Two of these ıstained a myocardial infarction within 24 hours, and ne died. Because of persistent pain, two other patients nderwent intraaortic balloon pumping, with immeiate relief of symptoms.[8] Both underwent coronary ypass grafting and both are alive. Coronary arteriogıphy showed that three of these four patients had more han 75 percent obstruction in three vessels, while the ɔurth patient, a 73 year old man, had 90 percent obtruction of the left main coronary artery and had a fatal ıyocardial infarction shortly after coronary arteriogıphy.

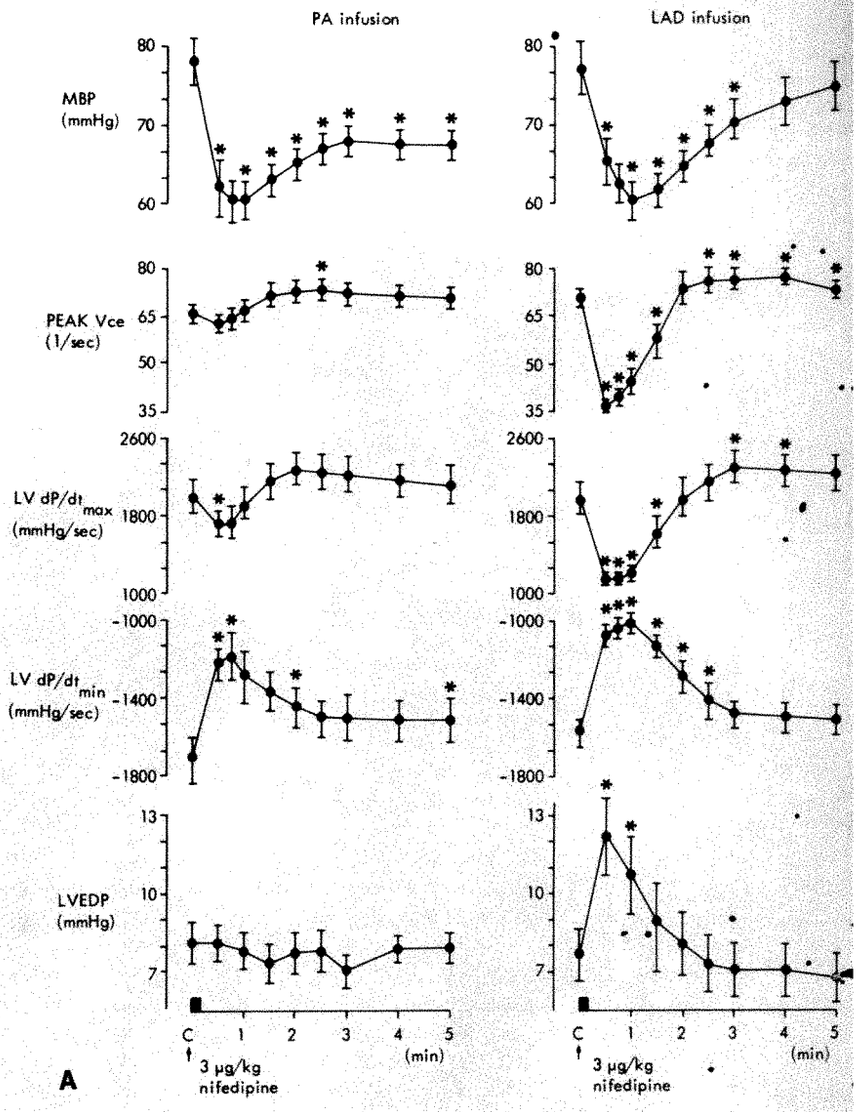
Twenty of the 27 patients who experienced initial elief of symptoms when nifedipine was added to the herapeutic regimen underwent elective coronary arıriography and left heart catheterization after they esumed some degree of physical activity in the interıediate care unit. However, one patient with postinırction angina (group III) sustained a fatal myocardial ıfarction before catheterization and within 7 days of ıitiation of nifedipine treatment. Of the 19 patients ndergoing catheterization, 1 had greater than 90 perent cross-sectional obstruction of the left main coroary artery and 9 had three vessel, 3 had two vessel and ix had one vessel coronary artery disease with greater han 75 percent obstruction.

Follow-up: In addition to the patient with fatal inırction, four other patients had a nonfatal infarction ıithin 2 weeks after the initial relief of symptoms. In wo of these patients, the event was related to angiogıphy; both had extensive pain, with ST-T changes and slight rise in cardiac enzyme levels but without new) wave formation. In one of the other two patients oronary arterial spasm was documented during angiography and injection of nifedipine into the involved coronary artery led to immediate relief.

Thus, of the total group of 27 patients who were managed with nifedipine and who became asymptomatic, 5 sustained an infarction (fatal in 1) within 2 weeks after initial stabilization. During further follow-up (3 to 5 months) no other instances of myocardial infarction were noted. Thus far, 15 of the 19 patients who underwent catheterization have undergone elective coronary bypass grafting. In these patients, the indication for operation consisted of a past history of unstable angina and an advanced degree of coronary arterial stenosis. All are alive and well. The other 11 patients have remained asymptomatic and have been maintained on nifedipine therapy.

Discussion

Effect of nifedipine on coronary spasm and on myocardial contraction (local contractile arrest in presence of increased coronary flow): The two parts of this study were carried out in patients with proved or suspected coronary arterial spasm. From the data in Table I, there is little doubt that in the majority of patients, direct intracoronary injection of nifedipine yields prompt relief when spasm can be demonstrated. Other authors,[2–6] using a variety of techniques, have demonstrated that this calcium blocking agent has a similar beneficial action. In addition, the data shown in Figures 4, 5, and 8 indicate that locally administered nifedipine acts directly on the myocardium. Measurements of the changing distances between radiopaque markers placed on the epicardium (Fig. 5) indicate that major changes in wall motion take place as early as 30 seconds after injection of nifedipine. The distance between the markers is substantially increased, with a reduction in regional shortening to approximately 67 percent of the control value. The rate of systolic shortening is significantly diminished, indicating a slowing of the local contractile process; the separation between the marker



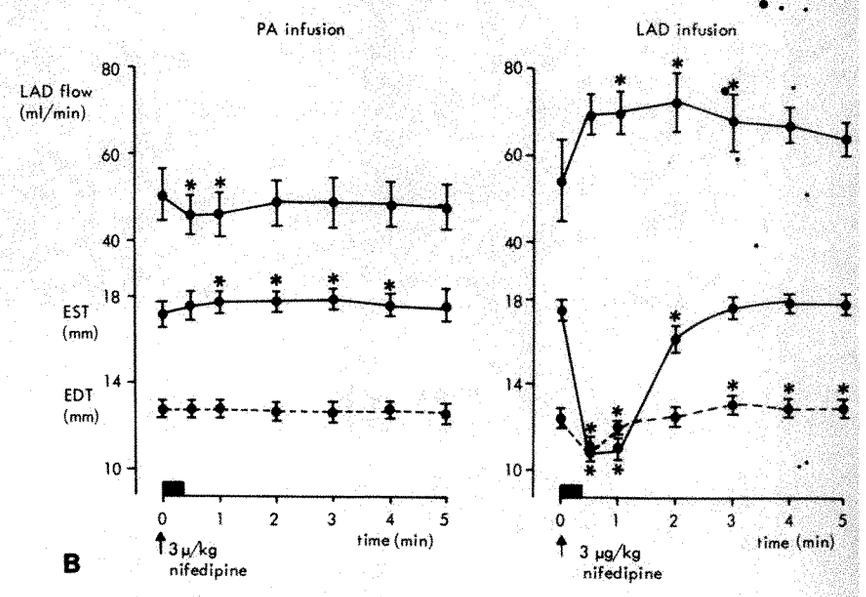


FIGURE 6. A, Hemodynamic changes after administration of 3 μg/kg of nifedipine into the pulmonary artery (PA) and into the left anterior descending coronary artery (LAD) of the same pig. Note that the effects on mean arterial blood pressure (MBP) and the rate of fall of left ventricular pressure (LV dP/dt_{min}) are independent of the site of injection, whereas the magnitude of the effects on myocardial contractility (peak V_{ce} and LV dP/dt_{max}) and ventricular filling pressure (LVEDP) are dependent on the site of the injection. The heart was paced at 104 beats/min.* $P < 0.05$ compared with baseline. **B,** left anterior descending coronary arterial (LAD) blood flow (from an electromagnetic flowmeter) and myocardial wall thickness after administration of 3 μg/kg of nifedipine into the pulmonary artery (PA) and the left anterior descending coronary artery. Injection into the pulmonary artery had no effect, that into the left anterior decending artery caused a transient decrease, mainly in end-systolic thickness (EST). After 3 minutes, a rebound in end-diastolic thickness (EDT) was observed (0.5 mm larger than baseline value). *$p < 0.05$ compared with baseline value.

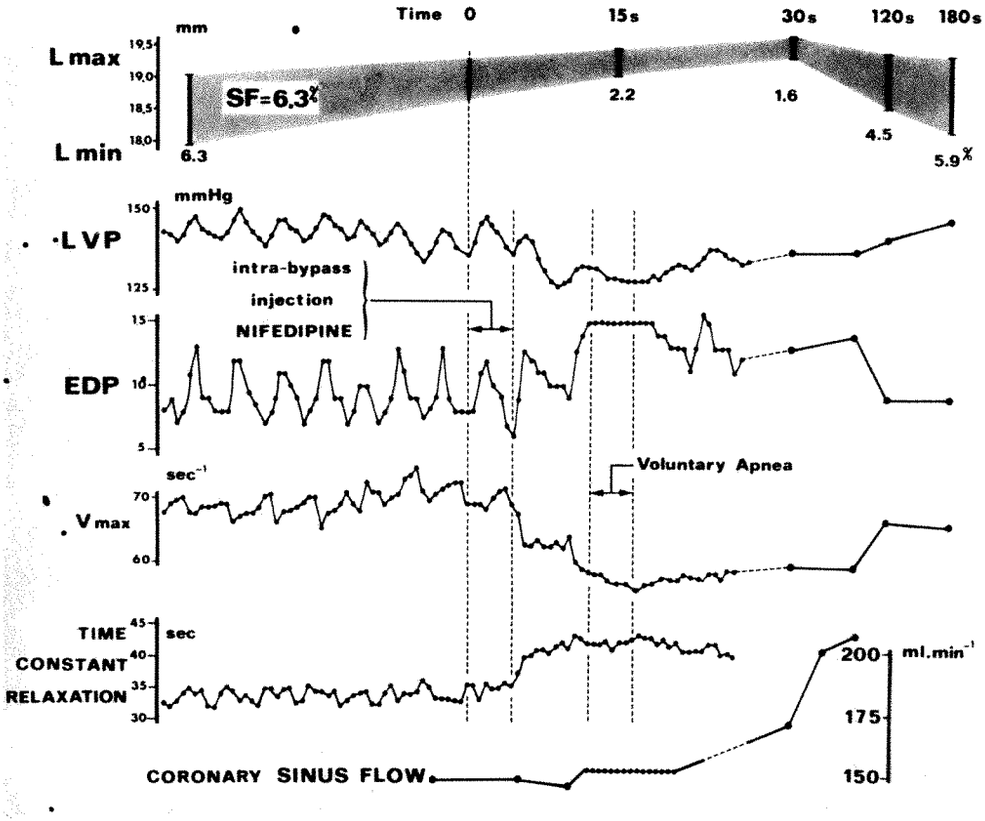


FIGURE 7. Continuous plot of marker distance (L_{max}, L_{min}) with shortening fraction, left ventricular pressures (LVP and EDP), V_{max} and the relaxation time constant of the region perfused by an injection of nifedipine into a patent bypass graft. In this patient, coronary sinus flow was measured continuously. Shortly after intrabypass injection of nifedipine, the shortening fraction (SF) decreased from 6.3 to 2.2 percent, accompanied by a rapid rise in end-diastolic pressure and decreases in V_{max} and left ventricular peak pressure. Simultaneously coronary sinus flow increased from 150 to more than 200 ml/min.

pairs reaches a minimum 80 ms after closure of the aortic valve, indicating that contraction became prolonged; in fact, at the peak of action of nifedipine, 38 percent of total regional shortening took place during early diastole of the ventricle as a whole. None of these changes were seen when marker distances were measured in the same patient in areas not perfused by nifedipine.

These observations complement published results from studies performed in our laboratory in the open chest pig[9] when nifedipine, in a dose of 3 μg/kg, was administered over 20 seconds into the left anterior descending coronary artery (Fig. 6). In these animals, coronary arterial flow, measured simultaneously from an electromagnetic flowmeter, showed a marked increase during the first 3 minutes after injection, and systolic thickening of the ventricular wall decreased from 18 to 11 mm during the same time. In other words, end-diastolic thickness decreased, systolic thickening was virtually abolished, and the process of contraction became extended into what is early diastole for the remainder of the ventricle. Yet, at the same time, flow in the left anterior descending coronary artery increased by 40 percent above its control value. None of these changes occurred in animals when the same dose of drug was infused into the pulmonary artery.

Similar findings have been documented in several patients. Data from one of these patients (Fig. 7), measured beat by beat over a period of 300 seconds, clearly show the immediate effect of nifedipine on ventricular wall dimensions, end-diastolic pressure, and V_{max}. Perhaps most important, in terms of the mechanism of action of the drug, the relaxation time constant increased by some 50 percent. All of these values could also be reliably measured during a period of voluntary apnea, showing that respiratory influences were minimal. The effects of nifedipine were maximal 30 seconds after injection, at which time the shortening fraction was barely 1.6 percent and V_{max} was at its lowest, yet coronary sinus blood flow had increased 200 ml/min. These appear to be extremely favorable responses for the ischemic myocardium.

These human and animal experiments complement each other and indicate that there is marked local contractile "arrest" in the presence of increased coronary flow. These data also complement those originally presented by Grün and Fleckenstein[13] and Vater,[14] who demonstrated that similar doses of nifedipine led to significant reductions in myocardial oxygen consumption in regions perfused by the coronary artery into which the drug had been injected.

Beneficial effects of nifedipine therapy for unstable angina: This series of observations, indicating an "oxygen-sparing" effect of nifedipine, led to our use of the drug in patients with unstable angina (Fig. 8 and 9). Indeed, the hypothesis has been put forward that the subset of patients with suspected coronary arterial spasm may receive no benefit from beta adrenergic blocking agents, and Yasue et al.[4] have specifically argued against their use in this group of patients. Rather, when beta adrenergic blockade has failed to relieve symptoms—despite its reduction of heart rate and

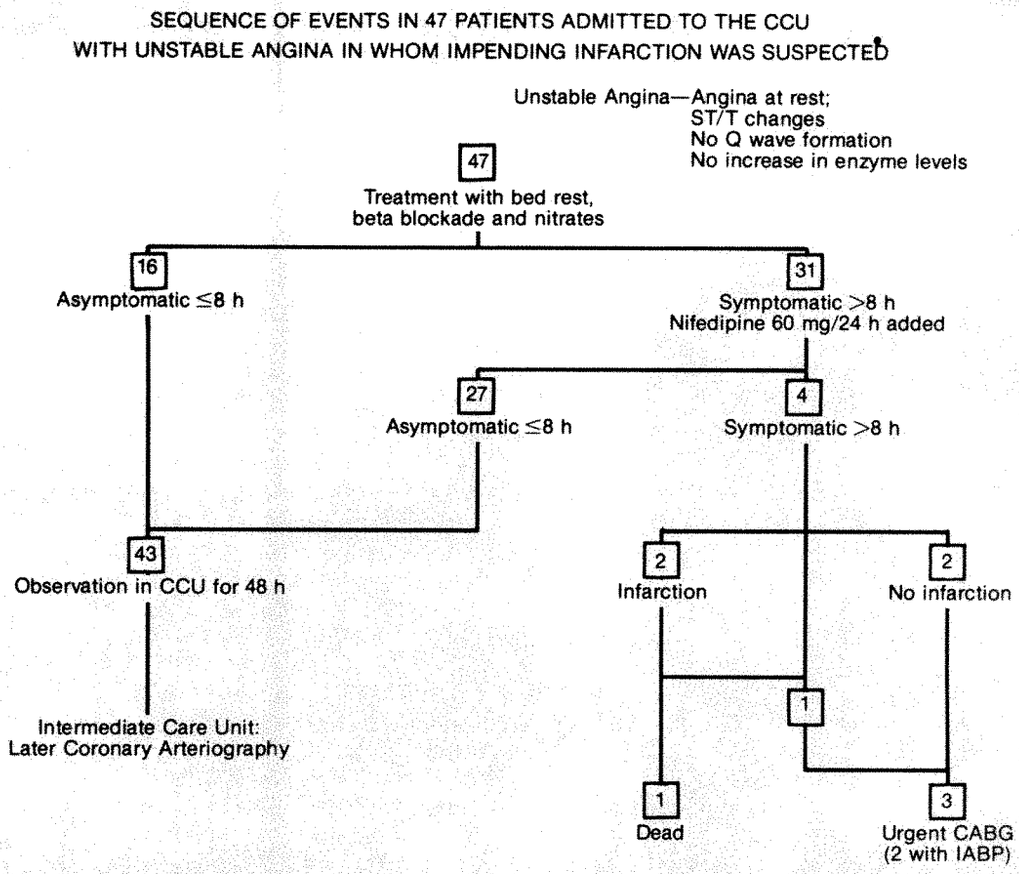


FIGURE 8. Schematic view of developments in 47 patients with suspected impending myocardial infarction. CABG = coronary arterial bypass grafting; CCU = coronary care unit; IABP = intraaortic balloon pumping.

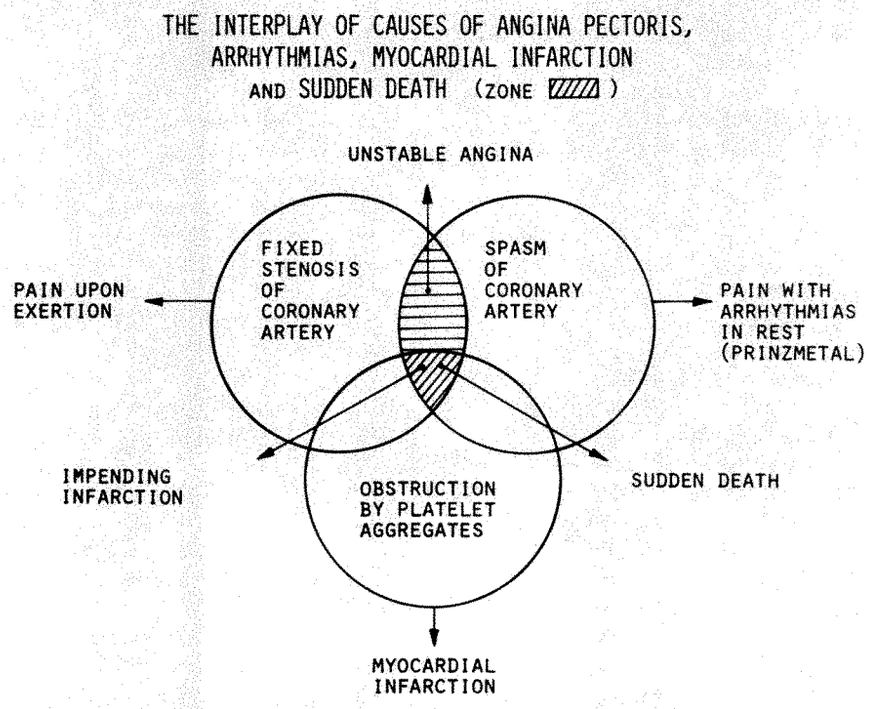


FIGURE 9. Schematic view of the interplay of the three main causes of unstable angina: fixed stenosis of coronary arteries, coronary arterial spasm, and coronary arterial obstruction by platelet aggregates. Nifedipine appears to have its most useful application in the **horizontally hatched area.**

ompetitive blocking at beta receptor sites—the addi-ion of nifedipine, or perhaps the use of nifedipine alone, nay be the more logical approach. Theoretically, the nhibition of transmembrane calcium influx into cardiac nuscle fibers results in less phosphate-bound energy eing transformed into mechanical work by calcium-lependent myofibrillar adenosine triphosphate (ATP), vhich in turn leads to a reduction in cardiac oxidative netabolism; oxygen need is therefore diminished. In ddition, the reduction in the calcium-dependent con-ractile tone of the larger epicardial coronary arte-ies—and perhaps to some extent the capillaries as vell—indicated by the sudden reduction of ventricular vall thickness (Fig. 6B) leads to increased flow and thus apidly restores the regional oxygen concentration to ıormal. In addition to these changes, dilation of large eripheral arteries will diminish afterload and may re-ult in a further, indirect reduction in cardiac oxygen lemand.

Henry et al.[15] have indicated that even when an area ıround an infarct is rendered ischemic, a reduction in he quantity of ischemic cells can be achieved with ni-edipine. In those patients in our group who did not espond to beta adrenergic blockade, nifedipine pro-luced similar dramatic and sudden results. Although his study was not randomized and in many other re-pects did not meet the requirements of a strict clinical rial, the reduction in symptoms was impressive. Twenty-seven of the 31 patients treated with nifedipine n addition to beta blocking agents became asymp-omatic within a very short period of time and remained o in nearly all instances. Given the brittle clinical state f these patients, and the failure of all other supportive herapy, it is highly likely that nifedipine was respon-ible for the improvement. In fact, in the four patients n whom nifedipine did not evoke a similarly favorable esponse, the extent of fixed organic stenosis, as dem-nstrated on coronary arteriography, was severe enough hat the lack of response to a spasmolytic agent was ıardly surprising. The subsequent response of these atients to intraaortic balloon pumping and emergency ypass surgery underscores that their obstructive le-ions were mainly of an organic nature. Under these onditions, the action of nifedipine may well be less pecific and unique.

Role of coronary spasm in unstable angina in resence of severe atherosclerotic disease: In this egard it is of interest to examine the coronary arterio-raphic findings in 20 of the 27 patients who responded romptly to nifedipine and to discuss briefly the rate f myocardial infarction. One patient with postinfarc-ion angina died 7 days after admission to the coronary are unit, just before the planned catheterization. Au-opsy showed extensive three vessel disease, including arrowing of the left main coronary artery. As indicated arlier, of the remaining 19 patients, 1 had greater than 0 percent narrowing of the left mainstem, and 9 had hree vessel disease, 3 had two vessel disease and 6 had ne vessel disease with more than 90 percent obstruc-ion. To date, 15 of these 19 patients have undergone bypass grafting and 4 sustained a nonfatal myocardial infarction before they could be operated on—in immediate relation to the cardiac catheterization procedure in 2 and after discharge from the hospital in 2. The 15 patients operated on are asymptomatic and no longer receive nifedipine therapy; the 11 patients not operated on are also asymptomatic but still receive nifedipine therapy.

These findings indicate the presence of severe atherosclerotic coronary artery disease in 14 of the 20 patients studied. It is suggested that the symptoms in the remaining 6 patients approximate those of Prinzmetal's syndrome although the complete manifestations thereof could not be observed during the acute phase. Because of the prompt response to nifedipine, spasm would seem to have been the dominant mechanism. In those patients with a long-standing history of coronary artery disease and severe atherosclerotic disease spasm probably played only a secondary role, although it was equally responsive to nifedipine.

Therapeutic failures and occurrence of myocardial infarction: In the four patients who did not respond to nifedipine therapy the rapidity of the subsequent events suggests that treatment with nifedipine had commenced too late. Five of the 27 patients who responded to nifedipine nevertheless sustained an infarction in the subsequent weeks compared with 2 of the 4 nonresponders. Because 1 of the 5 responders had had a previous infarction (group III) and in 2 (both from group II) the infarction occurred during coronary arteriography, nifedipine therapy can be considered to have failed in only 2 (7.4 percent) of the 27 patients in the longer term. This incidence relates favorably to the generally quoted incidence of myocardial infarction, which ranges from the 13 percent in the Rotterdam IMIR study[17] to 23 percent reported by Vakil,[18] in these severely ill patients with impending infarction. Incidentally, in our study the two responders to nifedipine with subsequent infarction had three vessel disease during coronary arteriography.

Therapeutic implications: We believe that nifedipine should be added to beta adrenergic blocking drugs when the latter show no immediate effectiveness in patients presenting with angina at rest. The combination of nifedipine and a beta blocking agent has not been shown to cause any adverse hemodynamic effects. In our opinion, nifedipine deserves further clinical evaluation for use in unstable angina.

Nifedipine inhibits myocardial contractility while increasing coronary blood flow and this combination of actions may help prevent myocardial infarction in patients who have unstable angina with a substantial vasospastic component (Fig. 9). However, those patients with advanced fixed organic obstructions do not respond as well.

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Treatment of Prinzmetal's Variant Angina

Role of Medical Treatment With Nifedipine and Surgical Coronary Revascularization Combined With Plexectomy

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This study describes three forms of treatment of Prinzmetal's variant angina. Coronary spasm, frequently found at coronary arteriography in patients with Prinzmetal's variant angina, can be treated with intravenous or intracoronary injection of nitroglycerin as well as of nifedipine. Nifedipine (0.2 mg) was injected directly into the involved artery in 12 patients and suppressed spasm in 9; in 3 patients, nifedipine increased coronary sinus flow, which had been decreased by spasm in one of the branches of the left coronary artery.

Patients with Prinzmetal's variant angina who have spasm superimposed on atherosclerotic lesions can benefit from coronary arterial bypass grafting combined with partial denervation of the heart. This combination yielded acceptable results (83.4 percent favorable outcome); recurrence of attacks occurred in only 6.7 percent of this group. In those forms of angina in which spasm occurs in angiographically normal coronary arteries, therapy is essentially medical. In 13 patients treated with oral nifedipine (30 to 40 mg/day), suppression of attacks was achieved in 11 instances. During the period of treatment, the methergine provocative test, which had been consistently positive before treatment, converted to negative in 12 patients. Transient withdrawal of nifedipine caused recurrence of pain in two patients.

Over the past 5 years, it has been demonstrated that the treatment of Prinzmetal's angina differs from that of typical angina pectoris. Beta adrenergic blocking agents, effective in the treatment of typical angina, do not achieve similar results in Prinzmetal's angina[1–4] and may even intensify anginal attacks.[5,6] Surgical treatment, when feasible, provides poorer results in Prinzmetal's angina than in the other forms of angina pectoris; that is, the rates of mortality and perioperative infarction are higher,[7,8] the number of occluded grafts is larger, and the recurrence of attacks is common.

One reason for these differences may be the presence of coronary arterial spasm. The incidence of spasm in Prinzmetal's angina has been variously estimated to be between 20 and 87 percent.[9,10] Among 70 patients with variant angina, we have observed spasm to occur spontaneously in 46 instances, an incidence rate of 66 percent. However, since the advent of provocative testing,[11] the incidence of spasm has been found to be considerably greater; among 45 patients recently examined, for example, we observed spasm in 42, an incidence rate of 93.5 percent. Thus, spasm appears to be an important and frequent phenomenon in Prinzmetal's angina.

Various drugs have been used to abolish the spasm observed during coronary arteriography. We have proved the usefulness of nifedipine

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when it is injected directly into the coronary vessel affected, and the first part of this paper will describe this observation.

Long-term treatment of patients with Prinzmetal's angina depends on whether the spasm is superimposed on fixed organic atherosclerotic lesions or whether it occurs in angiographically normal arteries. Among 70 of our patients with Prinzmetal's angina, 20 (29 percent) had angiographically normal coronary arteries; the remaining 50 (71 percent) had fixed atherosclerotic lesions. The arteriographic status of the coronary arteries should be kept in mind when long-term treatment is considered.

Methods

Selection of patients: All patients in this study fulfilled the following criteria for variant angina pectoris: recurrent angina at rest associated with S-T segment elevation (greater than 2 mm) in leads other than those reflecting an area of an old infarction, with return of the S-T segment to control levels after relief of pain and without evolution of myocardial infarction as manifested in serial electrocardiograms or cardiac enzyme determinations. All patients underwent coronary arteriography. The procedure included left ventricular cineangiography performed in the 30° right anterior oblique projection, and selective coronary arteriography was performed in six projections for the left coronary artery and five projections for the right coronary artery.

When spontaneously occurring coronary arterial spasm was not observed, a provocative test was performed according to a technique previously described.[12] The test consisted of a single intravenous injection of 0.4 mg of methergine, an ergot alkaloid similar to ergonovine maleate. The methergine challenge was repeated in several patients either at the time of arteriographic examination of the grafts or in an intensive care unit in accordance with the technique described by Nelson et al.[13]

The present study included 55 patients with variant angina who were separated into three groups:

Group A: Treatment of coronary spasm with direct injection of nifedipine into the affected coronary artery: This group included 12 patients with Prinzmetal's variant angina. Three of these patients experienced spontaneous spasm during coronary arteriography and in nine others spasm was induced by the provocative test. Spasm occurred in the left anterior descending artery in four patients, in the right coronary artery in three and in the left circumflex artery in four; in one patient it involved two arteries (left anterior descending and circumflex coronary arteries). After documentation of the spasm, nifedipine (0.2 mg) was injected directly into the affected vessel. If the spasm persisted for more than 2 minutes, nitroglycerin was injected intravenously. In three patients, coronary sinus blood flow was measured according to the technique described by Ganz et al.[14] before and during methergine-induced spasm and after intracoronary injection of nifedipine.

Group B: Treatment of Prinzmetal's angina by plexectomy associated with aortocoronary bypass grafting: This group included 30 patients with variant angina who ranged in age from 40 to 70 years. On coronary angiography 15 of these patients had significant obstruction of one vessel, 6 of two vessels and 9 of three vessels. All 15 patients had lesions considered suitable for coronary bypass grafting. Coronary arterial spasm was observed in 19 patients; spasm was spontaneous in 6 patients and was provoked by methergine in 13 others. The surgical procedure combined coronary bypass grafting with denervation of the heart to prevent recurrence of spasm. The denervation (plexectomy) was carried out before the bypass grafting and included four steps:

1. To avoid spasm induced by manipulating Wrisberg's ganglion (sympathetic fibers in the subaortic and retroaortic areas), a large bolus dose of lidocaine was infiltrated just beneath the root of the aorta.
2. The adventitia overlying the aorta was peeled from the left vagus laterally, to the most anterior aspect of the ascending aorta, medially.
3. Meticulous resection of all the ganglia and nerves located under the aortic root in Wrisberg's space was performed; this included resection of the entire triangular shaped tissue located between the trachea and the ascending aorta.
4. Dissection of the space between the descending aorta and the main pulmonary trunk and resection of the nerves to the right coronary artery.

Thus, resection of as much as possible of the major cardiac plexus located anteriorly near the base of the aorta and under the aortic root was performed. Cardiopulmonary bypass was started and conventional aortocoronary bypass grafting was carried out. Fifteen patients received a single coronary graft, six received two grafts and nine received three grafts. Patients were followed up in accordance with the following criteria: (1) clinical response; (2) resting electrocardiogram and 24-hour ambulatory electrocardiographic monitoring; and (3) provocative test with methergine.

Group C: Treatment of Prinzmetal's angina in patients with angiographically normal coronary arteries: This group included 13 men with variant angina who ranged in age from 21 to 74 years. Coronary arteriography revealed totally normal coronary arteries in eight patients and minimal irregularities with no significant stenoses in five. Provocative tests with methergine were performed in all 13 patients. Coronary arterial spasm in seven patients was localized to the right coronary artery, in two patients to the left anterior descending artery and in three to the left circumflex coronary artery. In one patient spasm involved both the left anterior descending artery and the circumflex artery. Ten patients were treated with 30 mg of nifedipine/day and three received 40 mg/day. Treatment was continued for an average period of 15 months (3 to 29) with six patients receiving nifedipine therapy for more than 1 year. Patients were followed up in accordance to the criteria for patients in group B.

Results

Treatment of coronary spasm with direct injection of nifedipine into the affected coronary artery (Table I): In eight patients, spasm disappeared completely within 2 minutes of the intracoronary injection of nifedipine. In one patient, spasm involved two vessels (left anterior descending and left circumflex arteries) and was attenuated but not entirely suppressed, and it was necessary to inject nitroglycerin to achieve complete relief. In three patients, injection of nifedipine had no effect, and when the spasm persisted beyond 2 minutes, nitroglycerin was injected intravenously. This maneuver abolished the spasm rapidly and completely. The vasodilator action of nifedipine injected into the affected artery seems to be of short duration. In one patient, methergine-induced spasm of the right coronary artery disappeared after injection of nifedipine into the affected vessel. Ten minutes later, spasm was induced in the same vessel with 0.4 mg of methergine; however,

TABLE I

Results of Injection of Nifedipine Into the Coronary Artery in 12 Patients With Spasm

Case	Spasm	Location of Spasm	Nifedipine Effect	Nitroglycerin Effect
1	Provoked	LAD 100%	+	
2	Provoked	LAD 100%	−	+
3	Provoked	LAD 100%	+	
4	Provoked	RCA 100%	+	
5	Provoked	RCA 100%	+	
6	Provoked	LCx 75%	−	+
7	Provoked	LCx 100%	+	
8	Provoked	LCx 100%	−	+
9	Provoked	LAD 75%, LCx 75%	+/−	+
10	Spontaneous	RCA 75%	+	
11	Spontaneous	LAD 75%	+	
12	Spontaneous	LCx 100%	+	

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; + = spasm relieved; − = spasm not relieved.

subsequent injection of nifedipine into the left coronary artery did not relieve the spasm. These results suggest that the drug has a direct effect, but this hypothesis remains to be confirmed by further studies.

In the three patients whose coronary sinus blood flow was measured before and during methergine-induced spasm, the latter was observed to occur in the left anterior descending artery (two patients) and in the left circumflex artery (one patient). During spasm, the flow decreased; after injection of nifedipine, the flow increased and exceeded baseline levels.

Treatment of Prinzmetal's angina by plexectomy associated with aortocoronary bypass: During the immediate postoperative period, 2 of the 30 patients died (surgical mortality 6.7 percent); 1 death was related to a low cardiac output, and 1 patient died with an intractable arrhythmia. One patient exhibited new Q waves in the electrocardiogram during the perioperative period. Of the 28 patients who survived operation, all were alive at the end of the follow-up period which averaged 23 months (range 3 to 48). At the end of the follow-up period all but two patients were asymptomatic and the latter had neither syncope nor heart failure. Two patients had recurrent attacks of angina. Recatheterization was carried out in 12 patients in order to evaluate the patency of grafts and in them all 14 grafts were patent. The methergine challenge was repeated in 21 patients. The challenge was performed at the time of arteriographic examination of the grafts in 12 patients or in the intensive care unit in accordance with the technique described by Nelson et al.[13] in 9 patients. In 20 patients the test did not provoke coronary arterial spasm or S-T segment change. In one patient who experienced recurrent attacks 3 months after the operation, coronary arteriography demonstrated that the graft, a bypass of the left anterior descending artery, was patent but spasm with S-T segment elevation could be induced by the provocative test. This patient was given nifedipine (40 mg orally/day) together with isosorbide dinitrate. He became asymptomatic, and further provocative testing was unable to induce electrocardiographic changes.

Treatment of Prinzmetal's angina in patients with angiographically normal coronary arteries: Treatment with nifedipine was continued for an average of 15 months (3 to 29) (Table II). Adverse effects were observed in two patients: One complained of cutaneous paresthesias and heat sensation but did not require discontinuation of therapy; the other experienced nausea and vomiting that necessitated withdrawal of the drug after 8 months of treatment.

Complete suppression of anginal attacks was achieved in 11 of 13 patients. Because of gastrointestinal intolerance, one patient had to discontinue therapy, whereupon the attacks recurred. Another patient had to interrupt treatment transiently and he also had a recurrence of attacks that disappeared completely when treatment with nifedipine was resumed.

Clinically, therefore, it may be concluded that highly satisfactory results were achieved during administration

TABLE II

Arteriographic Findings and Long-Term Follow-Up Study in 13 Patients With Prinzmetal's Variant Angina and Angiographically Normal Coronary Arteries

Case	Age (yr) & Sex	Site of Spasm	Nifedipine (mg/day)	Follow-Up (mos)	Pain-free	Persistent Attacks	Methergine Tests (n)
1	57M	LCx	30	24	Yes	No	3, neg
2	48M	LAD	30	6	Yes	No	2, neg
3	46M	LCx	30	12	Yes	No	1, neg
4	56M	LAD + LCx	30	21	Yes	No	4, neg
5	55M	RCA	40	4	No	Yes	1, pos
6	36M	RCA	30	8	No	Yes	1, neg
7	46M	RCA	30	17	Yes	No	1, neg
8	47M	LAD	40	12	Yes	No	4, neg
9	49M	RCA	30	26	Yes	No	4, neg
10	21M	RCA	30	19	Yes	No	5, neg
11	74M	RCA	30	3*	Yes	No	1, neg
12	59M	RCA	30	12	Yes	No	2, neg
13	45M	LCx	40	29	Yes	No	3, neg

* Patient had adverse reaction to nifedipine.

LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; neg = negative; pos = positive; RCA = right coronary artery.

of nifedipine in 11 of 13 patients. However, since it is well known that ischemic attacks, as documented by electrocardiographic monitoring, can occur in the absence of pain, the additional use of continuous Holter monitoring is justified. In all but one patient, a 24-hour electrocardiogram failed to show any evidence of ischemic attacks. The only patient whose attacks recurred in association with S-T segment elevation was one of the two patients whose anginal pain persisted. The provocative test was repeated in the 13 patients, with several being challenged two or three times during the follow-up period (32 tests). In 12 patients, electrocardiographic changes could not be induced by intravenous injection of 0.4 mg methergine. All of these patients had previously had a positive provocative test. Only one patient, who had had persistent pain and ischemic attacks during Holter monitoring, showed significant S-T segment elevation associated with pain.

Discussion

Intracoronary nifedipine versus nitroglycerin for acute coronary spasm: It is well known that arterial spasm observed at coronary arteriography can be suppressed with the administration of nitroglycerin, given either orally or, preferably, by intravenous injection. We have observed that when this drug was injected directly into the coronary artery affected by the spasm, it was abolished rapidly. In light of these results, we have studied the action of nifedipine injected directly into the vessel undergoing spasm. The initial results are promising. They show that when selectively injected into a coronary artery, nifedipine acts as a powerful vasodilator capable of suppressing spontaneous or methergine-induced spasm. However, from our limited experience, nifedipine seemed to show a slight delay in relieving spasm when compared with nitroglycerin. Moreover, since 3 out of 12 patients with coronary artery spasm did not respond to intracoronary nifedipine, it can be concluded that intracoronary nitroglycerin is the preferred treatment of these patients.

Surgical treatment of spasm in presence of fixed coronary stenosis: The long-term treatment of patients with Prinzmetal's angina depends on the arteriographic status of the coronary arteries. When coronary arteriography shows evidence of atherosclerotic lesions with or without superimposed spasm, two possibilities may be considered: (1) If the lesions are not operable (distal lesions, a narrow or stenosed vascular bed downstream, poor ventricular function), only medical treatment, that is, calcium antagonists and nitrates, should be employed. (2) If the lesions are amenable to coronary bypass surgery, the decision to operate is still subject to controversy.

The results of surgical treatment of Prinzmetal's angina are not as favorable as in angina pectoris on effort. Limet's review[15] of the published data showed that 33 percent of 214 patients had poor results; death and acute myocardial infarction each occurred in 11 percent. Rates of graft occlusion were much higher in these patients than those operated on for chronic stable angina pectoris. However, of greatest importance, anginal attacks persisted in a large number of patients. Clinically favorable results were obtained in only about 50 percent of patients. One possible reason for this difference between the results of patients with Prinzmetal's angina and those obtained in chronic stable angina may be the persistence of coronary spasm despite bypass surgery, causing obstruction of the vessel distal to the grafts. We have observed this phenomenon on two occasions. However, persistence of anginal pain may also be due to spasm occurring in another artery that may have appeared normal on preoperative arteriography.

It therefore appears reasonable that treatment of Prinzmetal's angina associated with fixed organic lesions should have a double aim: (1) to bypass the fixed lesions and (2) to suppress the spasm. Various authors[6–16] have suggested that Prinzmetal's variant angina is characterized by dysfunction of the autonomic nervous system. We recently observed that manipulation of Wrisberg's ganglion induced S-T segment elevation in two patients with Prinzmetal's angina. Thus, it appeared appropriate to consider combining coronary arterial bypass grafting with partial denervation of the heart in order to prevent the recurrence of spasm.[17] This surgical procedure, first described by Arnulf,[18] was employed in two patients with Prinzmetal's angina by Grondin and Limet.[8] Their two patients remained asymptomatic for more than 12 and 18 months, respectively. The results obtained in our series of 30 patients confirm their preliminary findings and suggest that plexectomy associated with aortocoronary bypass grafting could improve the results of surgical treatment in variant angina with organic narrowing. However, the plexectomy must be well performed. The rich network of fibers explains why plexectomy can be incomplete, especially as in relation to the posterior plexus, and an incomplete resection can explain the recurrent attacks observed in one of our patients. Nevertheless, these preliminary results should be interpreted with caution because of obvious difficulties in evaluating the effects of treatment of Prinzmetal's angina, which is characterized by considerable spontaneous variability of symptoms. Therefore, randomized trials of this procedure will be of considerable interest.

Oral nifedipine for prevention of spasm in normal coronary arteries: In the absence of stenotic lesions, treatment is confined to the prevention of coronary arterial spasm, which appears to be the key factor in triggering the attacks. Various drugs have been used in this subgroup of patients with angina—phenoxybenzamine,[19–21] atropine,[2–19] long-acting nitrates and verapamil[21] and amiodarone[22]—but treatment currently involves primarily the administration of calcium antagonists.

Spasm may be caused by various factors leading to contraction of the smooth muscle fiber, which depends on the calcium concentration in the medium. The usefulness of calcium antagonists in the treatment of Prinzmetal's angina has been reported in different studies.[20,23,24] Our results are similar to those obtained by Heupler and Proudfit[23] and Goldberg et al.[24] in coronary spasm refractory to other types of therapy. A European Cooperative study including 159 patients also

found that nifedipine prevented the recurrence of attacks in 75 to 83 percent of patients with Prinzmetal's variant angina. The results obtained with nifedipine in Europe are similar to those obtained by Hosoda and Kumura[25] and Endo et al.[2] More recently, Waters et al.[26] reported a rise in the threshold of response to an ergonovine challenge after administration of nifedipine.

Clinical implications: Although still undefined just a few years ago, a strategy for the treatment of Prinzmetal's angina is beginning to emerge. The basic therapy for spasm that occurs during coronary arteriography is the intravenous or, preferably, the intracoronary injection of nitroglycerin. However, our experience shows that intracoronary injection of nifedipine in a 0.2 mg dose can also have beneficial effects in these circumstances. Patients with Prinzmetal's angina who have fixed atherosclerotic lesions with superimposed spasm appear to benefit from coronary arterial bypass grafting, provided that the latter is combined with measures to treat spasm. In our experience, treatment of spasm can be achieved by partial denervation of the heart. Complementary therapy with nifedipine after coronary bypass grafting may be a useful approach, but the effectiveness of this combination of therapeutic modalities must be confirmed by a carefully performed study.

Calcium antagonists constitute the best therapy currently available for patients with Prinzmetal's angina with angiographically normal coronary arteries. Nifedipine was effective in 75 to 85 percent of these patients, as documented by the suppression of attacks, absence of signs of S-T segment changes during continuous electrocardiographic monitoring, and negative provocative tests for spasm. Nevertheless, our preliminary results must be regarded with caution, in view of the considerable spontaneous variability of symptoms in these patients, which accounts for the difficulty in evaluating therapeutic effectiveness in Prinzmetal's angina.

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Ergonovine Testing to Detect Spontaneous Remissions of Variant Angina During Long-Term Treatment With Calcium Antagonist Drugs

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A subgroup of 22 patients with variant angina who had responded well to calcium antagonist drugs were studied to determine if ergonovine testing could help assess the need for continued therapy. Before treatment all 22 patients exhibited angina with S-T elevation during ergonovine testing done in the coronary care unit according to a previously described protocol with sequential ergonovine doses of 0.0125, 0.025, 0.05, 0.1, 0.2, 0.3 and 0.4 mg administered at 5 minute intervals. After 9.4 ± 4.7 (range 1 to 24) months of treatment (nifedipine 7 patients, diltiazem 3, verapamil 8, perhexiline 3, nifedipine and diltiazem 1), all patients were free from anginal attacks. Medication was discontinued and ergonovine testing repeated 24 to 48 hours later (3 weeks for perhexiline). In 12 of the 22 patients, angina or S-T segment shifts did not occur during the second ergonovine test to a maximal dose of 0.4 mg. Treatment was not restarted in these patients and all 12 remain free of variant anginal attacks 4.2 ± 2.9 (range 1 to 13) months later. In seven patients angina and S-T elevation occurred during the second ergonovine test, in the same electrocardiographic leads as during the test before treatment. In three patients the ergonovine test induced angina with S-T depression in the leads where S-T elevation had occurred during the previous test. Treatment was reinstituted in these 10 patients with a positive test. No complications resulted from ergonovine testing in any patient.

We conclude that in many patients with variant angina, symptoms will disappear spontaneously and the ergonovine test will revert to negative. Treatment with calcium antagonist drugs can probably be safely discontinued in some patients with variant angina; ergonovine testing appears to be helpful in identifying such patients. Longer periods of follow-up are required to confirm that symptoms do not recur.

The natural history of variant angina has not been completely defined; however, Prinzmetal et al.[1] in their original description and others[2] have recognized that many patients eventually become asymptomatic for no apparent reason. This feature of the syndrome complicates the evaluation of any therapeutic intervention. Nevertheless, variant anginal episodes usually disappear in patients treated with calcium antagonist drugs[3–8] and do not recur during continued long-term treatment. After long asymptomatic periods of drug therapy, can calcium antagonists be safely discontinued in such patients? This question is particularly pertinent to patients who manifest adverse effects from calcium antagonist drugs; although treatment with nifedipine, diltiazem or verapamil is almost always well tolerated, perhexiline induces adverse effects in many cases during prolonged treatment.[5]

In our clinical experience we have attempted to taper and discontinue calcium antagonist therapy both in patients who manifest important adverse effects and in those who remain asymptomatic after many

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months or years of treatment. Attacks of variant angina do not recur in the majority of these patients and, when they do, reinstitution of treatment usually controls symptoms without permanent sequelae. However, in at least two of our patients acute myocardial infarction occurred soon after treatment with calcium antagonist drugs was decreased or discontinued.[9]

We therefore undertook this study in subsequent patients to determine whether ergonovine testing could provide useful data to assess the risk of discontinuing treatment with calcium antagonists in asymptomatic patients with previously active variant angina. Our previous studies[10] have shown that ergonovine testing can be safely performed in a coronary care unit environment with a high sensitivity in patients with active variant angina[10] and that the results of ergonovine testing during treatment with calcium antagonists correlate with the short-term clinical response to treatment.[7,11,12] The subgroup of patients selected for this study does not represent all patients with variant angina because only those who responded well to drug treatment are included.

TABLE 1

Clinical Data and Results of Ergonovine Tests in 22 Patients

Case	Age (yr) & Sex	Coronary Arteriography*	Site of ST↑	Control Ergonovine Test (dose in mg)	Treatment Period: Drug & Dose (mg)	Treatment Period: Ergonovine Test (dose in mg)	Treatment Period: Length of Treatment (mo)	Ergonovine Test With No Drug Treatment (dose in mg)	Repeated Test With Drug Treatment (dose in mg)	Follow-up Period: Drug & Dose (mg)	Follow-up Period: Duration (mo)
1	44F	LAD 40	L,V_1–V_5	ST↑ (0.025)	D 120	ST↑ (0.3)	7	Negative	None	None	1
2	59F	RCA 80	2,3,F	ST↑ (0.05)	V 160	ST↑ (0.4)	10	Negative	None	None	1
3	42M	LAD 50	V_1–V_5	ST↑ (0.025)	D 120, N 30	Negative	7	Negative	None	None	2
4	60F	LAD 75†, RCA 40	2,3,F	ST↑ (0.1)	P 400	ST↑ (0.2)	18	Negative	None	None	4
5	38M	Normal	2,3,F	ST↑ (0.3	P 300	ST↑ (0.3)	20	Negative	None	None	1
6	35M	LAD 75	V_1–V_3	ST↑ (0.05)	N 20	Negative	9	Negative	None	None	8
7	42F	Normal	V_1–V_4	ST↑ (0.1)	N 20	Negative	24	Negative	None	None	1
8	38M	LAD 70, RCA 75	V_1–V_3	ST↑ (0.3)	P 400	Negative	11	Negative	None	None	5
9	54F	LAD 40, RCA 30	2,3,F	ST↑ (0.4)	V 160	Negative	3	Negative	None	None	13
10	66F	Normal	2,3,F	ST↑ (0.05)	N 20	Negative	4	Negative	None	None	3
11	51M	LAD 30, RCA 30 LCx 40	3,F	ST↑ (0.2)	V 160	Negative	6	Negative	None	None	3
12	61F	Normal	2,3,F	ST↑ (0.3)	V 160	Negative	1	Negative	None	None	8
Mean	49.2						9.9				4.2
± SD	9.1						5.4				2.9
13	47M	Normal	I,L, V_1–V_6	ST↑ (0.2)	V 160	Negative	6	ST↑ (0.3)	Negative	V 160	4
14	33M	LAD 30, RCA 30	V_1–V_4	ST↑ (0.1)	D 120	Negative	6	ST↑ (0.1)	Negative	D 120	2
15	71M	LAD 85, LCx 85	V_2–V_4	ST↑ (0.1)	V 160	Negative	7	ST↑ (0.1)	Negative	V 160	2
16	51M	LAD 75†, LCx 80	V_1–V_2	ST↑ (0.05)	D 120	ST↑ (0.2)	5	ST↑ (0.2)	Negative	D 120	2
17	42M	RCA 35	2,3,F, V_5–V_6	ST↑ (0.025)	N 20	Negative	6	ST↑ (0.05)	Negative	N 20	14
18	50M	LAD 80†	V_1–V_3	ST↑ (0.05)	N 20	ST↑ (0.4)	7	ST↑ (0.4)	Negative	N 20	10
19	59F	Normal	2,3,F	ST↑ (0.2)	N 20	Negative	6	ST↑ (0.4)	Negative	D 120	5
20	60M	LAD 75	2,3,F, V_1–V_6	ST↑ (0.0125)	V 80	ST↑ (0.3)	13	ST↓ (0.2)	Negative	V 80	1
21	32M	LAD 40	1,L, V_1–V_6	ST↑ (0.1)	N 20	Negative	21	ST↓ (0.2)	ST↓ (0.3)	D 120	2
22	46F	Normal	1,L	ST↑ (0.1)	V 160	ST↑ (0.1)	9	ST↓ (0.3)	ST↓ (0.4)	V 160	6
Mean	49.1						8.6				4.8
± SD	± 9.1						± 3.4				± 3.2

* Numbers refer to percent luminal stenosis of each coronary vessel. † Coronary bypass graft to artery.
D = diltiazem; F = lead aVF; L = lead aVL; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; N = nifedipine; P = perhexiline; RCA = right coronary artery; SD = standard deviation; ST↑ and ST↓ = S–T segment elevation and depression; V = verapamil.

Methods

Study patients and treatment protocol: For the purposes of this study the diagnosis of variant angina was accepted in patients who exhibited short episodes of myocardial ischemic pain at rest associated with transient S-T segment elevation, reversible with nitroglycerin, in the absence of evidence of myocardial necrosis. Each of the 22 patients in this study had previously been hospitalized in the coronary care unit for a control ergonovine test followed by at least one drug treatment period including a second ergonovine test. The study protocol followed by the patients has been described in detail elsewhere.[7,11,12]

The dose levels of the oral calcium antagonist drugs used for treatment were those that in our experience optimally combine satisfactory efficacy with infrequent adverse effects: nifedipine, 20 mg every 6 hours; diltiazem, 120 mg every 8 hours; verapamil, 160 mg every 8 hours and perhexiline, 300 or 400 mg twice daily. In Patient 20 (Table I), the dose of verapamil was only 80 mg every 8 hours because sinus bradycardia and a junctional escape rhythm at 40 to 50/min were noted at higher dose levels. In Patient 3, variant anginal attacks could not be controlled with nifedipine, diltiazem or verapamil alone but disappeared with a combination of diltiazem, 120 mg every 8 hours; nifedipine, 30 mg every 6 hours; and nitrates.[13]

After hospital discharge, all but two patients were treated with one of the calcium antagonist drugs to which they had responded in the hospital (Table I). These two patients (Cases 4 and 5) showed clinical improvement and had negative ergonovine tests while taking nifedipine,[7] but were treated with perhexiline after hospital discharge because of a temporary shortage of nifedipine. All patients returned at regular intervals after discharge to be examined by one of us. Prophylactic treatment with nitrates was not routinely employed, except in Patient 3 as previously noted.

In 18 of the 22 patients, no episodes of angina at rest occurred after hospital discharge. In the other four (Cases 7, 17, 21 and 22), brief periods of chest pain at rest compatible with variant anginal episodes occurred infrequently, less than once a week, but without documentation of coexistent S-T segment changes. Because either the beneficial effect of drug treatment or a coincident spontaneous disappearance of variant anginal attacks could account for the clinical state of the patients, each was reassessed using ergonovine testing. In one patient (Case 12) the duration of treatment was only 1 month because of the appearance of adverse effects thought to be drug-related.

Ergonovine test procedure: All ergonovine tests were performed in an identical fashion according to a protocol described in detail elsewhere.[10,12] Cuff blood pressure and a 12 lead electrocardiogram were recorded at 1 minute intervals, beginning 2 minutes before the first drug dose and continuing for a minimum of 5 minutes after the last injection. At 5 minute intervals a bolus dose of ergonovine was administered intravenously in the following sequence: 0.0125, 0.025, 0.05, 0.1, 0.2, 0.3, and 0.4 mg. An intravenous bolus dose of 0.3 mg of nitroglycerin was injected as soon as there was an S-T segment shift of 1 mm or more from the control tracing. The test was considered negative if no S-T segment shift occurred up to the final ergonovine dose of 0.4 mg.

The sensitivity of this test procedure and the incidence of complications in our initial series of patients have previously been reported.[10] To date, 75 of the 77 patients with active variant angina who underwent ergonovine testing with this protocol manifested S-T segment elevation during the test. To determine whether the results of this ergonovine test procedure are reproducible, nine patients with active variant angina underwent a second test while taking no medication within 7 days of the original test; all nine exhibited angina and S-T elevation at the ergonovine dose identical or adjacent to that of the first test.[12]

No serious complications were noted in the original descriptions[14–16] of ergonovine administration as a diagnostic test during coronary arteriography; however, three deaths were subsequently reported.[17] No complications occurred as a result of ergonovine testing in the present study. Our total experience to date using this ergonovine test protocol comprises 171 positive and 297 negative tests. Death, transmural myocardial infarction, ventricular fibrillation, complete atrioventricular block or ventricular arrhythmias requiring antiarrhythmic drug therapy did not occur during or after any of these tests.

Testing protocol: Patients to be retested without nifedipine, diltiazem or verapamil after periods of outpatient treatment were instructed to discontinue the drug 24 to 48 hours before the time of the ergonovine test. In the three patients taking perhexiline, administration of the drug was stopped 3 weeks before the test. All patients were told to return to their regular drug regimen before the ergonovine test, if they experienced chest pain after discontinuing treatment with the drug, but angina did not occur in any patient. Patients returned to the hospital where the ergonovine test in the absence of drug treatment was carried out in the morning. If the test was negative (Cases 1 to 12) the patient was discharged that afternoon and did not resume drug treatment. In 10 patients (Cases 13 to 22) S-T segment abnormalities developed. In these patients a single dose of the patients' calcium antagonist drug was given and another ergonovine test was performed 90 minutes later, during the afternoon. After the latter test, the patient was discharged with continued treatment with a calcium antagonist drug. Eight of these 10 patients were retested with the same drug and dose they had previously taken; in Patient 19 the tested drug was changed to diltiazem because of a temporary shortage of nifedipine, and in Patient 21 the drug was changed from nifedipine to diltiazem because of occasional symptoms compatible with variant anginal attacks during preceding nifedipine treatment. After these studies all patients continued to return at regular intervals to be interviewed and examined by one of us.

Coronary arteriography: All patients had undergone coronary arteriography and left ventriculography before their first ergonovine test. Selective coronary arteriography was performed with use of a percutaneous femoral approach and preformed catheters, as previously described.[18] Particular care was taken to avoid catheter-induced coronary arterial spasm. No attempt was made during cardiac catheterization to induce coronary spasm by administering ergonovine. Nitroglycerin was not given before the initial injections; however, when a lesion was noted, the vessel was filmed again in several views after administration of sublingual nitroglycerin. The left ventricular angiogram was filmed in the 30° right anterior oblique view before coronary arteriography. All angiographic documents were routinely interpreted independently by an experienced cardiovascular radiologist. The coronary arteriographic findings are listed in Table I. On left ventriculography, Patient 16 had anterolateral and apical hypokinesia, Patient 11 had diffuse hypokinesia and Patient 15 had anterolateral akinesia; the other 19 patients had normal left ventricular angiographic findings.

Results

Ergonovine test before and during drug treatment: During the control ergonovine test before treatment all 22 study patients manifested angina and S-T elevation. In 15 of the 22, the S-T elevation occurred at an ergonovine dose of 0.1 mg or less (Table I). During the same hospitalization within a drug treatment period lasting several days, the ergonovine test became negative to the maximal dose of 0.4 mg in 14 of the 22 patients. In seven of the remaining eight patients the ergonovine test remained positive with S-T elevation, but only at the dose level of 0.2 mg or higher. In five of the eight patients whose test remained positive during the drug treatment period an ergonovine dose at least two levels higher than that during the control test was required to induce a positive response.

After hospital discharge episodes of variant angina could not be detected in 18 of the 22 patients; 4 patients (Cases 7, 17, 21 and 22) had infrequent episodes of chest pain at rest, less than 1/week. Because of this favorable evolution, all 22 patients underwent another ergonovine test without drug treatment to evaluate the need for continued drug therapy.

Repeated ergonovine test without drug treatment: In 12 of the 22 patients this repeated ergonovine test induced no S-T segment shifts up to the maximal ergonovine dose of 0.4 mg. In a further seven cases, angina and S-T elevation occurred during this test, always in the same electrocardiographic leads as during the original control ergonovine test before the start of treatment. The dose of ergonovine that induced S-T elevation was the same as that of the initial test in two cases and larger in the other five. In the remaining three patients the repeated ergonovine test without drug treatment induced angina with S-T segment depression in the leads that had shown S-T elevation during the initial ergonovine test. In each of these three cases the ergonovine dose required to cause S-T depression was larger than the dose required to induce S-T elevation in the original test.

The patients whose tests reverted to negative could not be differentiated by other clinical variables from those whose tests remained positive. The mean age (± standard deviation) of those with a negative test (49.2 ± 9.1 years), was similar to those with a positive test (49.1 ± 9.1 years). Patients with normal coronary arteriograms were equally distributed between the two groups (Table I). The test reverted to negative in 7 of 9 women but only 5 of 13 men (difference not statistically significant). The duration of treatment (9.9 ± 5.4 months) in patients with a negative test was similar to that of the group with a positive test (8.6 ± 3.4 months).

Follow-up: The 12 patients whose ergonovine test reverted to negative after discontinuation of drug treatment were not restarted on calcium antagonist drug therapy. Variant angina has not recurred in any of them after a mean follow-up period of 4.2 ± 2.9 months (range 1 to 13). One patient (Case 6) has mild, stable exertional angina.

The seven patients who exhibited angina with S-T elevation during the repeated test in the absence of drug treatment underwent a second test on the same day, 90 minutes after a dose of nifedipine, diltiazem or verapamil (Table I). Each of these tests with treatment was negative up to the maximal ergonovine dose of 0.4 mg. The three patients who exhibited angina with S-T depression during the repeated test after withdrawal of drug treatment were retested in a similar fashion. However, angina with S-T depression recurred in two of these three patients during the repeated ergonovine test with treatment.

Treatment with nifedipine, diltiazem or verapamil was continued in each of the 10 patients who had S-T segment shifts during the test without drug treatment. After a mean follow-up period of 4.8 ± 3.2 months (range 1 to 14) nine patients are entirely asymptomatic. Patient 22 continues to have infrequent episodes of pain at rest, as before, but without documented S-T changes.

Discussion

Role of ergonovine testing in variant angina: The administration of ergonovine during coronary arteriography has been shown to be a sensitive and specific diagnostic test for variant angina.[14–16] In patients with documented variant angina ergonovine almost always induces angina with S-T segment elevation.[14–16] If coronary arteriography is repeated while these findings are present, severe coronary spasm is invariably found.[14–16] Because the actual visualization of coronary spasm is usually unnecessary, ergonovine testing could theoretically be performed at a time other than during coronary arteriography. The feasibility and safety of ergonovine testing done in the coronary care unit according to a carefully defined protocol using small initial doses has been demonstrated.[10] With use of this protocol, the sensitivity of the test for the diagnosis of variant angina is high and the results of the test are reproducible.[10–12]

After the start of treatment with nifedipine,[7,11,12] diltiazem[11,12] or verapamil,[11,12] the ergonovine test in nearly all patients with variant angina is either negative, or positive at a higher ergonovine dose level than during the test before treatment. During short treatment periods lasting several days, the results of ergonovine testing correlate with the clinical state; that is, patients with a negative test or a test positive only at the dose level of 0.3 or 0.4 mg of ergonovine have infrequent variant anginal episodes or none at all, but patients with a test still positive at small doses of ergonovine usually continue to have frequent attacks.[7,12]

Role of ergonovine testing in determining when to discontinue treatment: These considerations suggest that the results of ergonovine testing might be useful in determining when to discontinue calcium antagonist drug therapy in asymptomatic patients with variant angina. Each of the patients in this study manifested angina with S-T elevation during the ergonovine test before treatment; in 14 of the 22, the re-

peated test at the start of treatment was negative. When the patients were restudied after an average follow-up period of 9 months, the ergonovine test performed in the absence of medication was negative in 12 cases. Treatment was not restarted in these patients and variant angina has not recurred over a subsequent follow-up period averaging 4 months. Thus, a negative ergonovine test appears to correlate with the absence of variant anginal attacks not only during drug treatment periods but also after treatment is stopped.

Longer follow-up periods are necessary to confirm that discontinuing administration of calcium antagonist drugs in these patients in this manner is entirely safe. The clinical course of variant angina is often characterized by abrupt variations in the frequency of symptoms, suggesting that variant anginal attacks might eventually recur in some of these patients.

Significance of S-T depression during ergonovine test: Of the remaining 10 patients who were retested after discontinuation of treatment, 7 manifested angina with S-T elevation as they had during their initial ergonovine test before treatment. However, the other three patients exhibited S-T depression in the same electrocardiographic leads in which S-T elevation had occurred during their first ergonovine test. Maseri et al.[19] have described S-T depression caused by coronary spasm in patients who at other times spontaneously demonstrated S-T elevation. In our experience nearly 100 percent of patients with active variant angina who have undergone ergonovine testing have exhibited S-T elevation during the test. The occurrence of S-T depression during the test likely represents a less severe degree of coronary spasm than would be present with S-T elevation. Stein et al.[20] described S-T depression after ergonovine administration in patients with coronary disease without variant angina; these findings may have been caused by the normal physiologic effect of ergonovine on peripheral and coronary resistance and not by focal coronary spasm. However, spasm probably caused the S-T depression in at least two of the three patients in our study because they did not have significant fixed coronary stenoses.

Significance of disappearance of symptoms after treatment: Do asymptomatic patients with a negative ergonovine test in the absence of medication still have variant angina? It is customary to think of variant angina as a permanent diagnosis and not as a transient phenomenon; however, as originally noted by Prinzmetal et al.,[1] symptoms often disappear entirely, particularly if myocardial infarction occurs. Although the clinical manifestations of variant angina are known to be caused by coronary arterial spasm, the mechanisms that induce spontaneous episodes of coronary spasm are unclear. Until the etiology of variant angina is better understood or until long-term follow-up studies of large numbers of patients are completed, the exact status of asymptomatic patients who previously had variant angina will remain unclarified.

From a practical point of view, the results of our study suggest that many patients with variant angina who are asymptomatic during long periods of treatment with calcium antagonist drugs may not require further therapy. Ergonovine testing appears to be an objective method of evaluating the clinical status of patients with variant angina.

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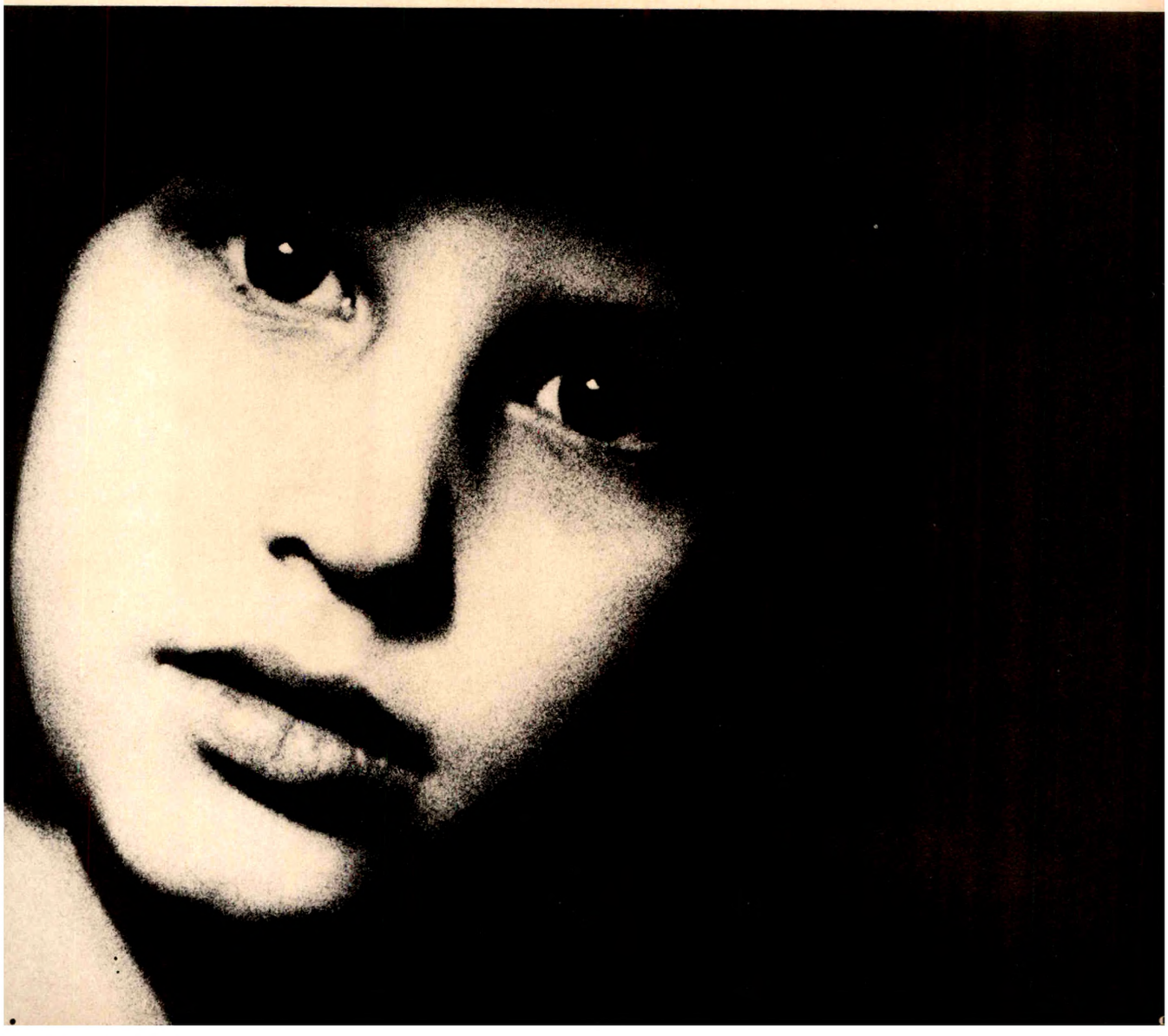

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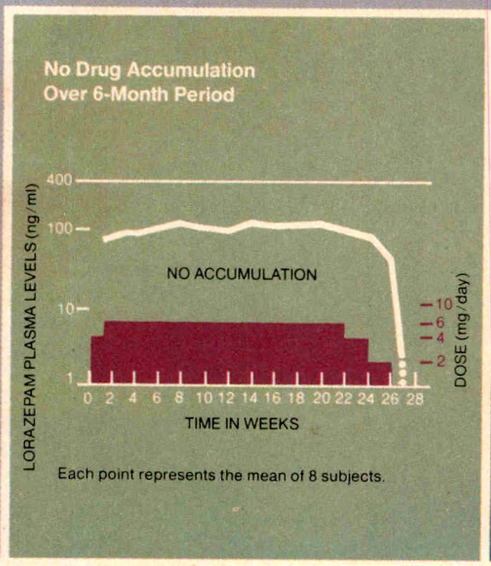

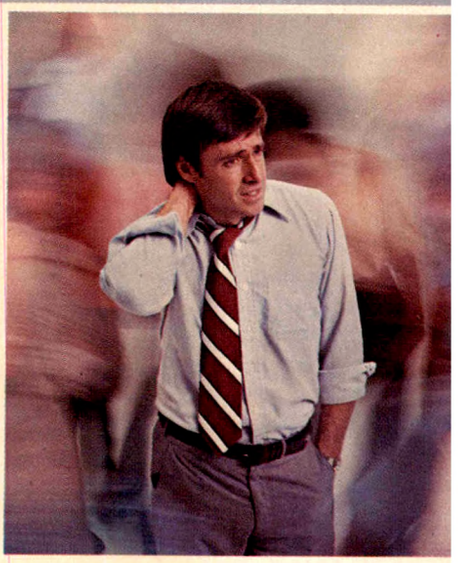

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Pharmacokinetics

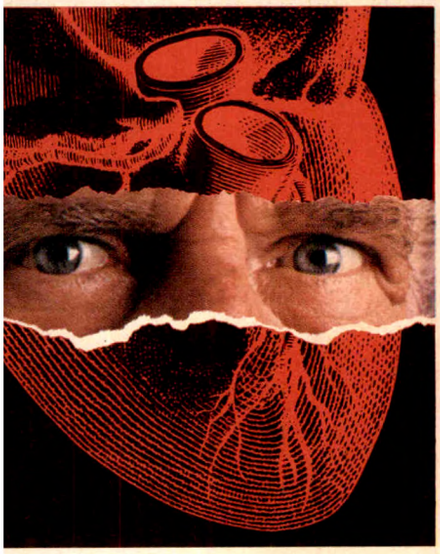
Ativan (lorazepam) is eliminated more rapidly than other benzodiazepines; generates no clinically active metabolites. The half-life of free lorazepam is about 12 hours; steady-state blood levels are attained in 2-3 days. (Comparable data for diazepam: 20-50 hours and at least 7-10 days.) Ativan shows no evidence of accumulation, even when given in high doses for as long as 6 months. (The pharmacokinetic profile of a drug can define such characteristics as absorption, distribution, metabolism and elimination but cannot, at present, be directly related to its therapeutic effectiveness.)

Anxiety neuroses

In many nationwide studies involving thousands of patients with anxiety neuroses, Ativan (lorazepam) consistently provided significant relief of anxiety, tension, agitation and irritability as measured by standard Hamilton, Global (physician rated) and 35-Item (patient self-rated) scales.

They're all about the same, aren't they? Until recently, that seemed to sum up the prevalent attitude about the benzodiazepines. After all, they all work similarly and all are effective anxiolytics. With seven of these compounds now available, however, differences have begun to emerge. Foremost among them: different metabolic pathways, which distinguish the relatively short-acting Ativan (lorazepam) from long-acting diazepam, clorazepate and chlordiazepoxide. At the same time, your choice can be made with confidence in the clinical record of Ativan, which confirms its value in anxiety neuroses and in significant anxiety associated with functional or organic disorders, as well as in older patients.

Consider the record of Ativan:



Anxiety in cardiovascular disorders

Ativan (lorazepam) has been specifically evaluated and found effective in seven common protocol, double-blind studies involving 423 patients (211 on Ativan) whose anxiety was related to organic and functional cardiovascular disorders. The cardiovascular component has not, of course, been shown to be significantly benefited by such therapy.

Anxiety in gastrointestinal disorders

So far, nine common protocol, double-blind studies of Ativan have focused on anxious patients with functional or organic gastrointestinal complaints (457 patients, 234 on Ativan). Ativan was clearly effective in reducing the anxiety of these patients. The gastrointestinal component has not, of course, been shown to be significantly benefited by such therapy.

Anxiety in the aging patient

Because its simple metabolism is not readily impaired with advancing age, and accumulation is not likely to present a problem, Ativan is a good choice for older patients. Those who have trouble swallowing solid medication appreciate the small Ativan tablet, which is tasteless and disintegrates within seconds in water or fruit juice.

Ativan® (lorazepam) for Anxiety

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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Nitrol®
(nitroglycerin ointment, 2%)

Description: Nitrol® Ointment contains 2% nitroglycerin (glyceryl trinitrate) in a special lanolin-petrolatum base. It is a prompt acting vasodilator, effective in the relief and prevention of anginal attacks.

Action: When the ointment is spread on the skin, the active ingredient (nitroglycerin) is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effect. Nitroglycerin ointment is effective in the control of angina pectoris, regardless of the site of application.

Indications: Prevention and treatment of angina pectoris attacks.

Contraindications: May be contraindicated in patients with marked anemia, increased intraocular pressure or increased intracranial pressure. Should not be employed in patients with known idiosyncrasies to nitrites.

Warning: In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

Precautions: A hypotensive headache is a sign of overdosage. Occasionally elderly patients may have no untoward symptoms while recumbent but may develop postural hypotension with faintness upon suddenly arising.

Dosage and Administration: For angina pectoris the ointment may be applied every 3 to 4 hours as required. The usual dose is 1 to 2 inches, as squeezed from the tube, although some patients may require as much as 4 or 5 inches. The ointment should be spread in a thin uniform layer on the skin. The optimum dosage is determined by starting with an application of ½ inch of ointment and increasing the dose in ½ inch increments each successive application until headache occurs, then decreasing to the largest dose which does not cause headache. Nitrol Ointment can be applied to any convenient skin area but psychologically, many patients prefer the chest.

Measurement and application of the ointment is easily accomplished with the aid of the specially designed Appli-Ruler™ supplied with the ointment. The ointment can be squeezed onto the graduated area of the Appli-Ruler and conveniently spread over the desired skin area. Keep the tube tightly closed and store at controlled room temperatures.

Caution: Federal law prohibits dispensing without prescription.

Supplied:
30 gram tube NDC 0091-5617-31
60 gram tube NDC 0091-5617-02
30 gram 6-Pack Unit NDC 0091-5617-61
60 gram 6-Pack Unit NDC 0091-5617-62

References:

1. Reichek, N, Goldstein, RE, **et al, Circulation, 50**:Aug. 1974.
2. Meister, SG, Engel, TR, **et al, Br. Heart J., 38**:10, 1976.
3. Taylor, WR, Forrester, JS, **et al, Am. J. Cardiol., 38**:Oct. 1976.
4. Parker, JO, **et al, Am. J. Cardiol., 38**: Aug. 1976.

Kremers-Urban Company
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The Original...
Nitrol® (nitroglycerin ointment, 2%)
Fills a therapeutic void
in your cardiology practice
Nitrol Ointment—the original topical coronary vasodilator—provides subjective symptomatic improvement for your angina patients; long-lasting freedom from pain and discomfort; possible reduction in oral medication requirements; decreased nocturnal attacks; overall symptomatic improvement.
The clinical efficacy of Nitrol has been confirmed in 12 published studies.
• supplements sublingual nitroglycerin medication
• provides consistently prolonged beneficial hemodynamic effects[1,4]
• produces sustained, enhanced exercise capacity; concomitant changes in heart rate and blood pressure—without evidence of tolerance or toxicity[1]
• decreases pulmonary wedge and arterial pressures plus systemic diastolic arterial pressures up to 5 hours[2]
• favorably affects peripheral vascular resistance, venous capacitance, preload and afterload[3,4]
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a Complete Family of Pacemakers.

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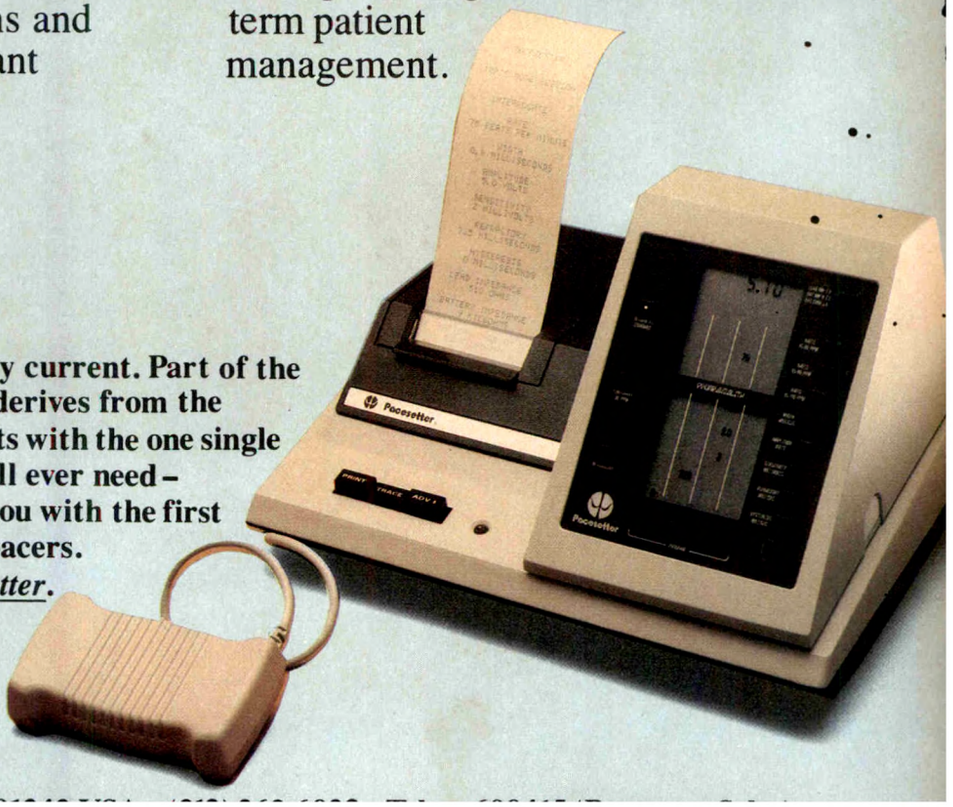

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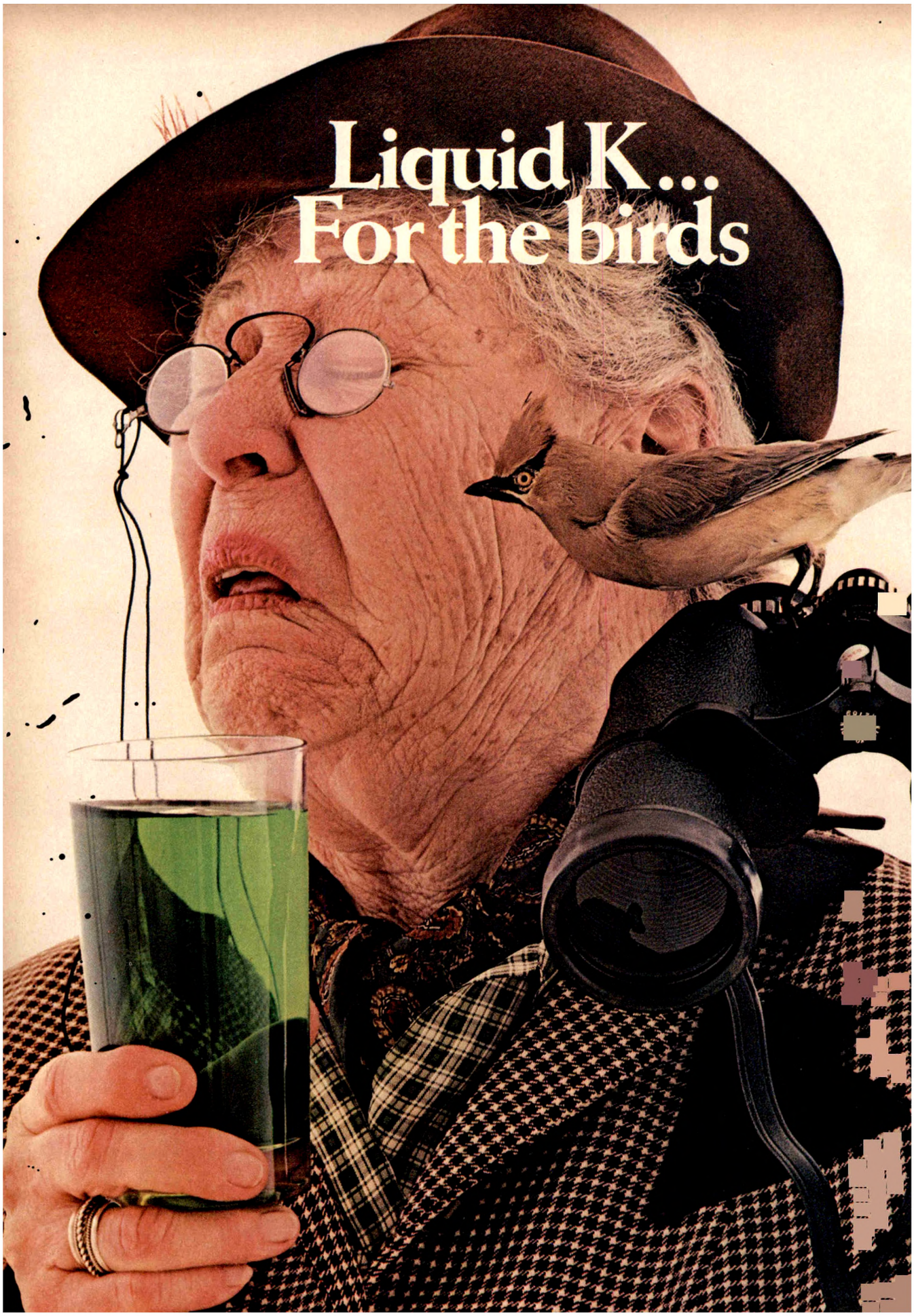
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Slow-K...
No squawks

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There are 5 years of U.S. clinical experience behind Slow-K. The 8 mEq tablet has proved safe and effective in over 4 million patients in the U.S. alone.*,†

25¢ a day

The cost of a day's therapy averages less than a quarter.‡

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Slow-K has an unparalleled record of patient compliance.

No taste problems

Patients prefer Slow-K to unpalatable liquid.

Salt of choice (KCl)

The preferred salt to correct the hypokalemic alkalosis that may result after long-term use of diuretics.

*Slow-release potassium chloride tablets should be reserved for patients who cannot tolerate or have compliance problems with liquid K preparations. The total number of GI lesions in both foreign countries and the United States remains less than one per 100,000 patient-years.

†Data on file, CIBA Pharmaceutical Company

‡Average cost per day based on Pharmaceutical Data Services audit.

4 million patients,
5 years of U.S. clinical experience†

Slow-K®

CIBA 165

potassium chloride slow-release tablets 8 mEq

Please turn page for brief prescribing information.

CIBA

SLOW-K®
potassium chloride slow-release tablets

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS
Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C78-23 (4/78)

Consult complete product literature before prescribing. 128-6089-A

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C I B A

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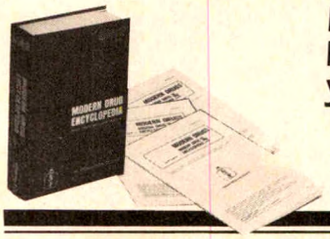

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The Frustrated Benevolence of "Dr. Anonymous"

PAUL KLIGFIELD, MD

New York, New York

Shortly after William Heberden published his original description of the clinical features of angina pectoris in 1772, he received an intriguing letter from an unnamed physician who suffered from the disease. The case of "Dr. Anonymous" is significant as the earliest account of ischemic heart disease clearly associated with ventricular arrhythmias. This astute observer not only predicted his own sudden death, but also offered his body in the benevolent hope that autopsy correlation would contribute to the understanding of the cause of angina pectoris.

The association of ventricular arrhythmias with sudden death in the setting of ischemic heart disease is currently well appreciated. Although many patients are aware of their cardiac rhythm irregularities, few describe their symptoms and occasional sense of impending doom as colorfully as did "Dr. Anonymous," an unnamed 18th century English physician who in 1772 recognized his own angina pectoris from reading Heberden's original account of the disease. The events surrounding this intriguing case of "Dr. Anonymous," who predicted his own sudden death, are an important and revealing chapter in the early history of knowledge of angina pectoris. This physician both provided us with one of the earliest clinical descriptions of ischemic arrhythmia and offered his own body for autopsy examination in the hope that a pathologic basis for the disease could be established.

More than 2 centuries ago, William Heberden of London (Fig. 1) introduced the original, masterful clinical description of angina pectoris in the second volume of the *Medical Transactions*.[1] "Some account of a disorder of the breast" was published in 1772, based on 20 cases presented to the College of Physicians in 1768, and later expanded by an additional 80 cases as a chapter in his *Commentaries on the history and cure of diseases* which appeared posthumously in 1802.[2]

Heberden received his medical degree at Cambridge in 1739 and became a highly successful London practitioner. Fluent in Latin, Greek and Hebrew, he was described by his illustrious patient Samuel Johnson as "ultimum Romanorum, the last of our learned physicians." In addition to his clinical account of angina, Heberden is known for his early descriptions of deforming arthritis of the hands, night blindness and varicella. In 1759 he collaborated with Benjamin Franklin in preparing a pamphlet on inoculation for use in the Colonies.

Heberden's description of angina pectoris clearly outlined the classic symptoms[1]:

> Those, who are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as if it would take their life away, if it were to increase or to continue: the moment they stand still, all this uneasiness vanishes . . . After it has continued some months, it will not cease so instantaneously upon standing still; and it will come on, not only when the persons are walking, but when they are lying down and oblige them to rise up out of their beds every night for many months together: and in one or two very inveterate cases it has been brought on by the motion of a

From the Division of Cardiology, Department of Medicine, The New York Hospital-Cornell Medical Center, New York, New York. Manuscript received July 8, 1980, accepted July 30, 1980.

Address for reprints: Paul Kligfield, MD, Division of Cardiology, The New York Hospital-Cornell Medical Center, 525 East 68th Street, New York, New York 10021.

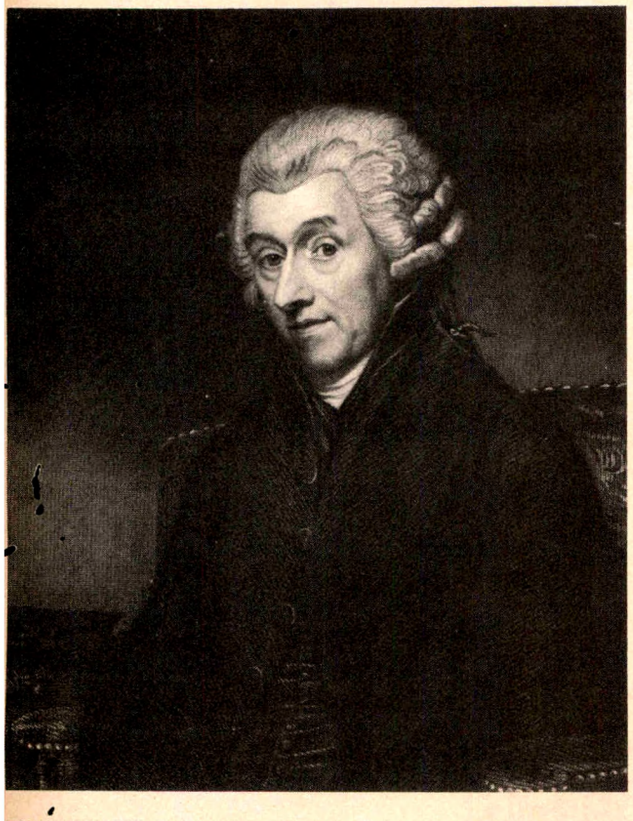

FIGURE 1. William Heberden, whose 1772 original description of angina pectoris prompted "Dr. Anonymous" to report his own intriguing case. After a portrait by Beechey.

horse or a carriage, and even by swallowing, coughing, going to stool or speaking, or by any disturbance of mind . . . .

Heberden was careful to make no unverified speculation regarding the origin of angina: "What the particular mischief is," he observed, "is not easy to guess, and I have had no opportunity of knowing with certainty." He was clearly aware of sudden death among patients with the disorder but had been unable to observe an autopsy. The reason, he explained, was that "most of those, with whose cases I had been acquainted, were buried, before I had heard that they were dead."

In April of 1772, shortly after publication of this account, Heberden received a letter from an anonymous English physician[3]: "I am now in the fifty-second year of my age," the writer explained by way of introduction, "of a middling size, a strong constitution, a short neck, and rather inclining to be fat." Regarding Heberden's recent description, he observed, "I found it to exactly correspond with what I have experienced of late years."

There is little doubt that this physician suffered from angina pectoris. "The first symptom is a pretty full pain in my left arm a little above the elbow," he noted, "and in perhaps half a minute it spreads across the left side of my breast, and produces either a little faintness, or a thickness in my breathing; at least I imagined so, but the pain generally obliges me to stop." Symptoms were precipitated by effort but never at rest. "It always attacked me when walking, and always after dinner," but never "in a morning, nor when sitting, nor in bed."

What made his case unusual, "Dr. Anonymous" informed Heberden, was associated sensations that "have frequently led me to think that I should meet with a sudden death." These symptoms, from a modern vantage point, must certainly have been caused by recurrent ventricular arrhythmias. "I have often felt," he wrote, "what I can best express by calling it an universal pause within me of the operations of nature for perhaps three or four seconds; and when she has resumed her functions, I felt a shock at the heart, like that which one would feel from a small weight being fastened by a string to some part of the body, and falling from the table to within a few inches of the floor." This vivid description suggests perception of the enhanced ejection that results from postextrasystolic potentiation after single or sequential ventricular ectopic complexes.

Convinced by this disturbing sensation that his death was imminent, "Dr. Anonymous" offered his body for examination and pathologic correlation under Heberden's supervision, hoping to "shew the cause of it; and, perhaps, tend at the same time to a discovery of the origin of that disorder, which is the subject of this letter, and be productive of means to counteract and remove it." As occasionally happens, this intimation of impending death was soon realized. The death of "Dr. Anonymous" within a half hour of the onset of symptoms occurred during an after-dinner walk. According to Heberden, "by a paper found in his will, if he died suddenly, he had desired that I might immediately have notice of it, in order to have the body opened and examined."

The autopsy was performed within 48 hours. Heberden's appreciation for the potential posthumous contribution of "Dr. Anonymous" to the understanding of angina is apparent. "I used my best endeavors," he reported, "that such a benevolent intention should not be frustrated, by procuring that experienced and accurate anatomist Mr. J. Hunter to open the body." John Hunter, then recently appointed surgeon to St. George's Hospital, was assisted in this examination by his pupil Edward Jenner.

Both the anonymous letter to Heberden and Hunter's postmortem findings were published in the third volume of the *Medical Transactions*.[3] Despite careful attention to the chest, Heberden noted that "no manifest cause of his death could be discovered." Although no abnormalities of the heart were found at the time, Jenner later reported to Caleb Hillier Parry[4] that the coronary arteries in this early important case of angina were not carefully examined. Thus, the benevolent intention of "Dr. Anonymous" that his death would provide direct insight into the underlying cause of angina pectoris was indeed frustrated. Yet his letter served to focus clinical attention on the need for clinical-pathologic correlation. Subsequent cases, involving Jenner

as investigator and Hunter as both investigator and victim of the disease, soon established the association with obstructive coronary lesions.[5]

Who was the astute and benevolent "Dr. Anonymous"? Recent examination of the Hunter manuscript case records by Dr. K. D. Keele[6] has identified a Dr. Haygarth of Chester as Heberden's previously unnamed correspondent. Haygarth's case is important as the earliest description of angina associated with significant cardiac arrhythmia. Further examination of the life and times of this physician, who anticipated his own sudden death from ischemic heart disease and made a noble effort to contribute to our understanding of its cause, will be of great interest.

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JANUARY THROUGH AUGUST 1981

1981

To be arranged individually — **Preceptorships in Cardiology.** Arthur Seizer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

JAN. 12–16 — **Twelfth Annual Cardiovascular Conference at Snowmass.** John H. K. Vogel, FACC, director and Bruce C. Paton, FACC, co-director. Opticon Theatre, Snowmass Resort, Snowmass, CO

FEB. 2–4 — **Clinical Echocardiography 1981—M-Mode, 2-Dimensional and Pulsed Doppler Techniques,** Pravin M. Shah, FACC, director and John S. Child, FACC, Joseph K. Perloff, FACC, and Maylene Wong, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

FEB. 9–11 — **Calcium (Slow Channel)-Inhibiting Drugs in Cardiovascular Therapy: Mechanism of Action and Application.** Borys Surawicz, FACC and Attilio Maseri, FACC, directors. New Orleans Marriott, New Orleans, LA

FEB. 19–20 — **Ventricular Arrhythmias and Sudden Cardiac Death.** Thomas B. Graboys, FACC and Bernard Lown, FACC, directors. Sheraton Boston Hotel, Boston, MA

MAR. 30–APR. 3 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Krannert Institute of Cardiology, Indiana University Medical Center, Indianapolis, IN

APR. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 16–18 — **New Diagnostic and Therapeutic Modalities in Cardiology.** Edmund H. Sonnenblick, FACC and James Scheuer, directors. Grand Hyatt New York, New York, NY

APR. 23–24 — **Contemporary Phonocardiography.** Morton E. Tavel, FACC, director. Methodist Hospital, Indianapolis, IN

APR. 27–MAY 1 — **Consultant's Course in Cardiology.** Richard Gorlin, FACC, Louis E. Teicholz, FACC, Simon Dack, FACC and Ephraim Donoso, FACC, directors. Mount Sinai Medical Center, New York, NY

APR. 29–MAY 1 — **Vectorcardiography—An Advanced Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

MAY 7–9 — **The Pathology of Acquired Heart Disease and of the Conduction System.** Jesse E. Edwards, FACC, Maurice Lev, FACC and Saroja Bharati, FACC, directors. Radisson Hotel, St. Paul, MN

MAY 7–9 — **Cardiovascular Emergencies.** Arthur Selzer, FACC and Richard Pasternak, co-directors. The Mark Hopkins, San Francisco, CA

MAY 7–9 — **Practical Cardiology for the Primary Care Physician,** Leonard S. Dreifus, FACC and Joel Morganroth, FACC, directors. Sarasota Hyatt Hotel, Sarasota, FL

MAY 13–15 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director and Antonio C. de Leon, Jr., FACC and John F. Stapleton, co-directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington, DC

MAY 14–16 — **Cardiac Diagnostic Techniques—A Clinical Perspective.** Arnold M. Weissler, FACC and Nicholas Z. Kerin, FACC, directors and Franklin E. Hull, FACC, S. C. Khullar, FACC and Melvin Rubenfire, FACC, co-directors. Detroit Plaza Hotel, Renaissance Center, Detroit, MI

MAY 18–22 — **Modern Cardiology.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Sheraton Atlanta Hotel, Atlanta, GA

MAY 28–31 **Sixth Annual Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Carillon Hotel, Miami Beach, FL

JUNE 17–19 **The Patient with Arrhythmia—A Clinical Approach.** Ross D. Fletcher, FACC and W. Proctor Harvey, FACC, directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington, DC

JUNE 30–JULY 3 **Eighth Annual Symposium on Clinical Echocardiography: Current Applications and New Developments.** Arthur D. Hagan, FACC, director and Anthony N. DeMaria, FACC and William F. Friedman, co-directors. Snowbird Conference Center, Snowbird Ski and Summer Resort, Snowbird, UT

AUG. 29–31 **Tutorials in the Tetons: Cardiac Emergencies—New Diagnostic and Therapeutic Advances (Seventh Annual).** Robert S. Eliot, FACC, director. Jackson Lake Lodge, Moran, WY

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LEARNING CENTER PROGRAMS: JANUARY to JULY 1981

Program Number	Date	Program Director	Title of Program
308	January 12–13	William Grossman, MD	The Role of the Cardiac Catheter in the Patient with Heart Disease
309	January 15–16	Winston E. Guam, MD and Samuel Kaplan, MD	Cardiac Electrophysiology and Rhythm Disorders in Pediatrics
334	February 5–6	August M. Watanabe, MD	Fundamental Cardiac Biochemistry for the Cardiologist
333	February 12–14	H. J. C. Swan, MD	Newer Concepts and Directions in the Treatment of Heart Failure Associated with Coronary Heart Disease
310	February 16–18	Sylvan Lee Weinberg, MD	Clinical Update for Nurses: The Coronary Care Unit and Acute Myocardial Infarction
311	February 23–25	William C. Roberts, MD	Congenital Heart Disease: The Multidisciplinary Approach
312	March 2–4	Nanette K. Wenger, MD	Rehabilitation of the Cardiac Patient
313	March 30–31	Jere H. Mitchell, MD	Cardiovascular Benefits and Risks of Exercise
314	April 1–3	J. O'Neal Humphries, MD	Coronary Heart Disease: New Management Methods
315	April 8–10	Victor Parsonnet, MD	Current Concepts in Pacing
316	April 13–15	Keith Cohn, MD	Exercise Testing: Diagnostic and Physiological Considerations
317	April 20–22	Pravin M. Shah, MD	Current Applications of Echocardiography: M-Mode, Two-Dimensional and Pulse Doppler Techniques
318	April 23–25	Daniel S. Berman, MD	Nuclear Cardiology
319	April 27–28	Leonard S. Dreifus, MD and Frits L. Meijler, MD	Computer Electrocardiology: Present Status and Hope for the Future
320	April 30, May 1–2	John A. Spittell, MD	Peripheral Vascular Disease
321	May 6–8	Marvin I. Dunn, MD	Electrocardiography for Critical Care Nurses
322	May 11–13	Abdul J. Tajik, MD and James B. Seward, MD	The Role of Two-Dimensional Echocardiography in the Clinical Practice of Cardiology
323	May 14–16	G. Charles Oliver, MD	Ubiquitous PVC
324	May 18–20	William J. Mandel, MD	His Bundle Electrocardiography: Contributions to the Clinical Understanding of the Electrocardiogram
325	May 28–29	Robert O. Brandenburg, MD	Cardiology for the Consultant
326	June 1–3	Shahbudin H. Rahimtoola, MD	Valvular Heart Disease
328	June 8–10 (tentative)	Borys Surawicz, MD	Changing Role of Electrocardiography in the Clinical Practices
327	June 11–13	Robert G. Tancredi, MD	Management of Pulmonary, Renal and Electrolyte Disorders in Cardiac Patients
329	June 15–17	Robert A. O'Rourke, MD	Detection of Cardiac Disease by Physical Examination
302	June 22–24	Paul C. Gillette, MD	Decisions in Clinical Pediatric Cardiac Surgery
331	June 29–30, July 1	B. Leonard Holman, MD	Nuclear Cardiology
330	July 8–10	Michael R. Rosen, MD	Clinical Pharmacology and Electrophysiology of Antiarrhythmic Drugs

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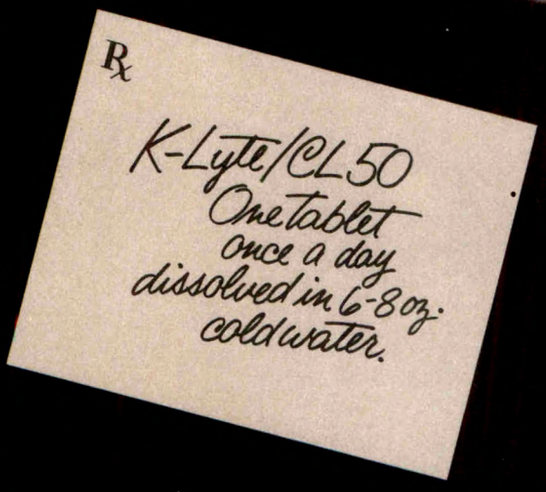

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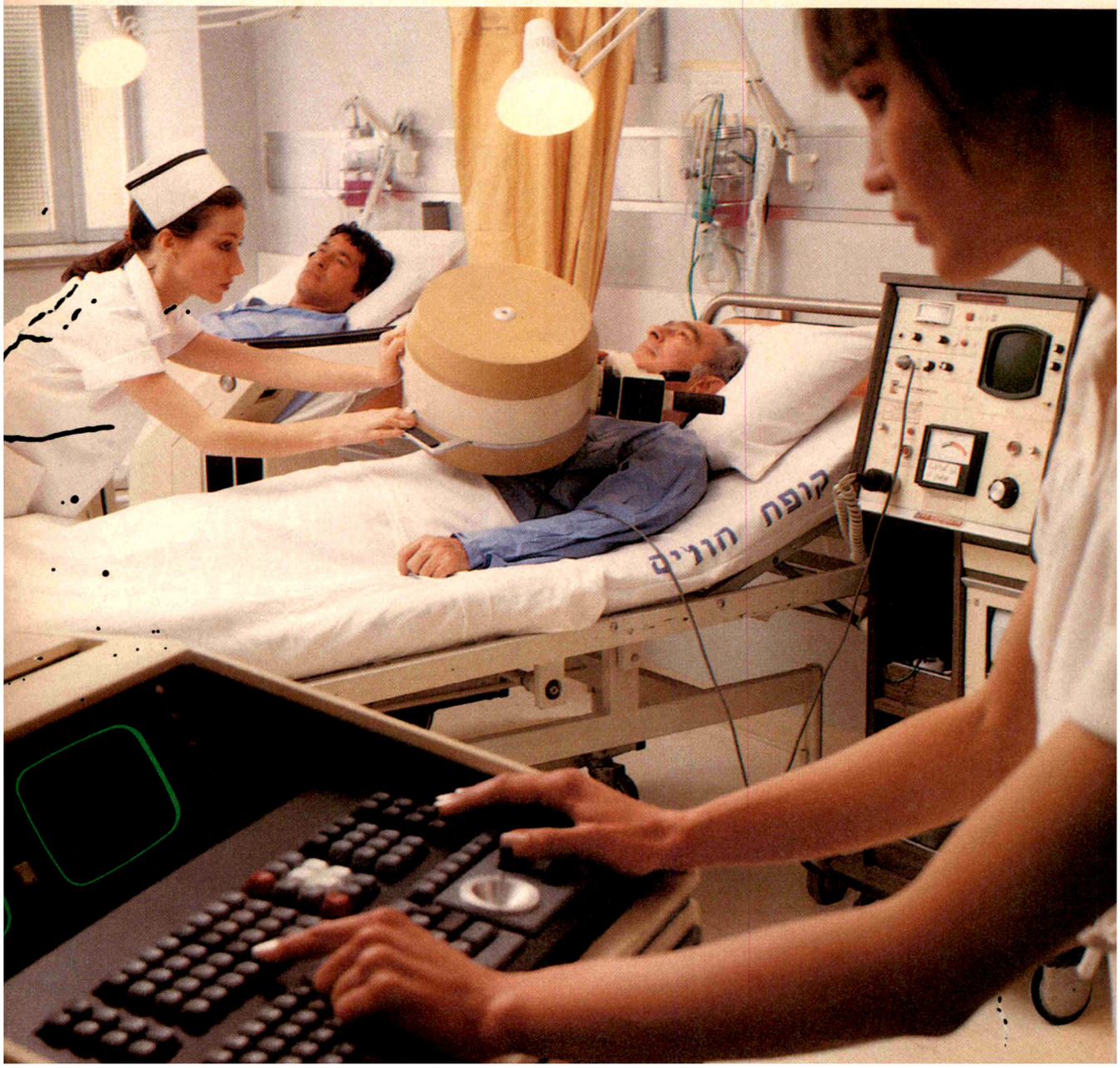

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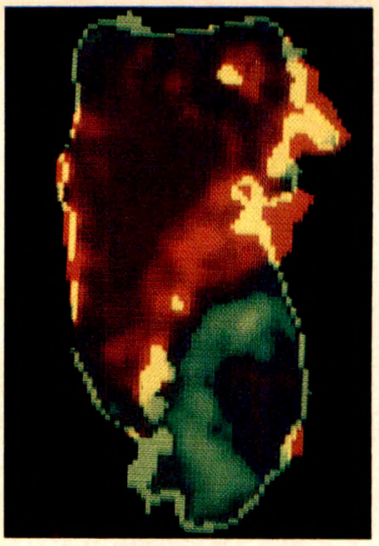

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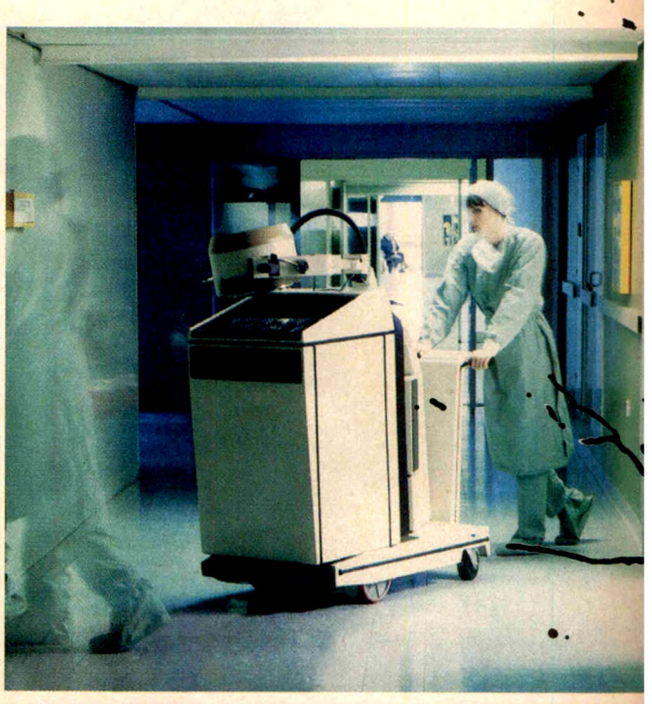

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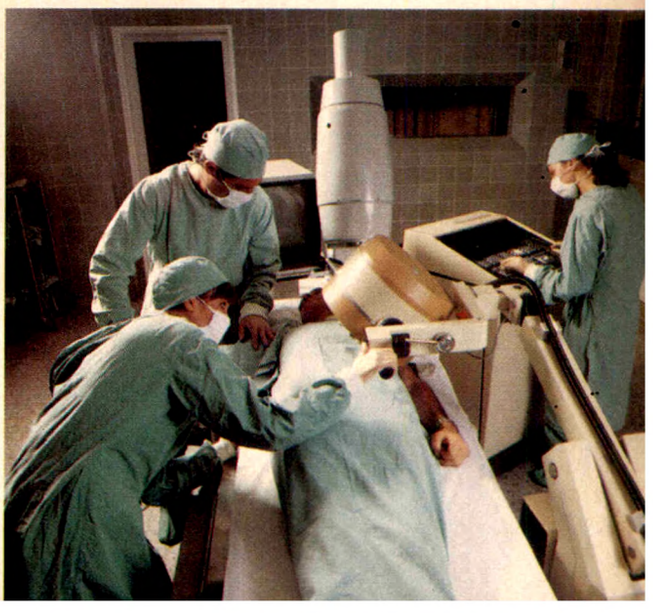

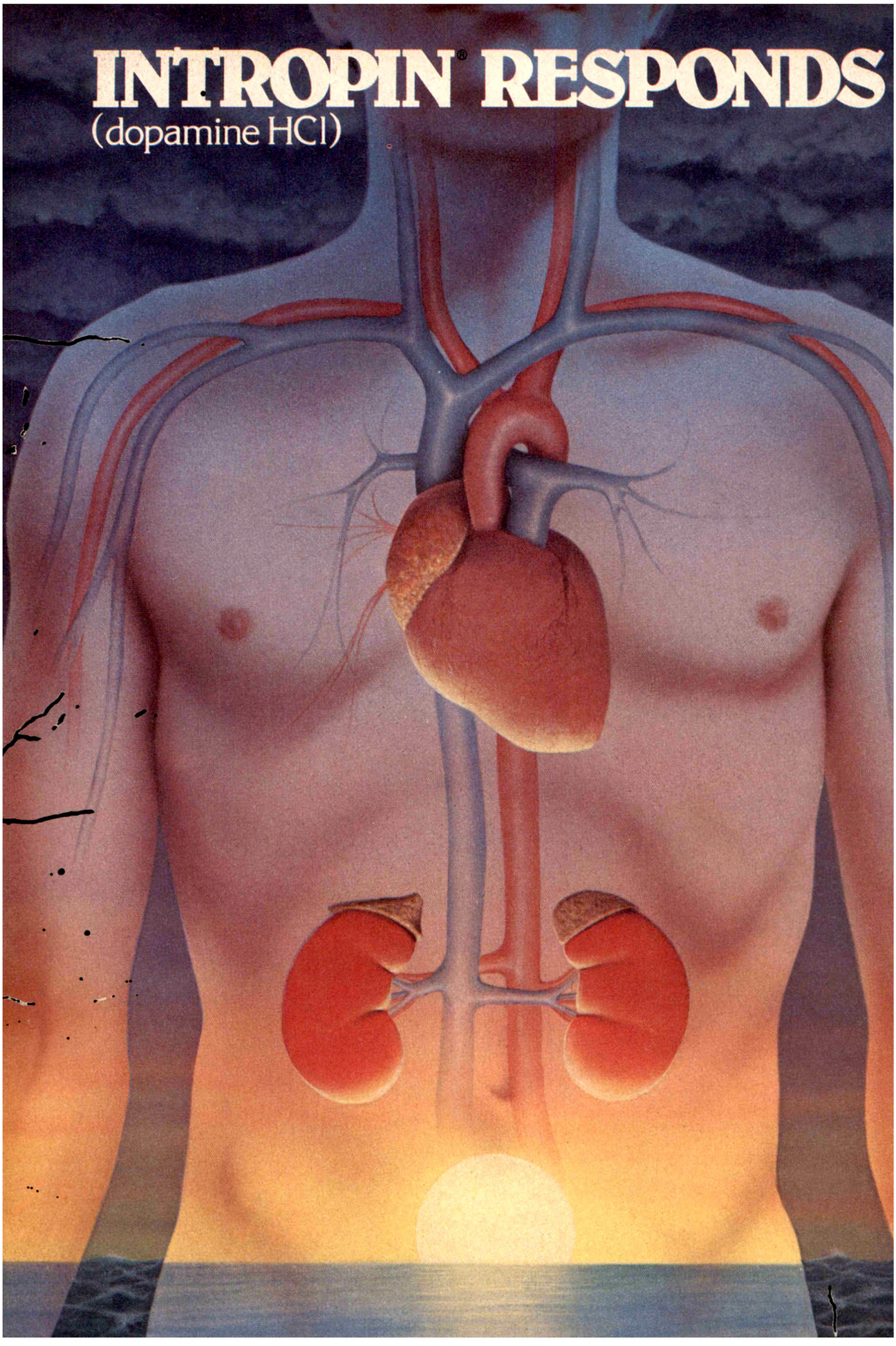
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(dopamine HCl)

MATCH CHANGING CONDITIONS IN SHOCK BY FINE-TUNING DOSAGE

tropin — at any oint time shock

other drug works like Intropin® opamine HCl) in "routing" blood ere it is needed, and when it is eded, to maintain vital organ rfusion. Careful dosage titration ovides the particular hemody- mic/renal effects you desire for given patient, at any point in e, over a wide range of shock mptoms.

nique dosage exibility... nique patient sponse

ghtly hypotensive patients h lo ut adequate cardiac out- t, fa urine output and duced vital organ perfusion ually experience increased urine w, modest increases in cardiac tput and reduced peripheral istance with low Intropin doses 5 mcg/kg/min).

derate hypotension, reduced rdiac output and venous return s further reductions in urine out- t are likely to respond to inter- ediate (5-20 mcg/kg/min) ropin doses by showing further creases in cardiac output, blood essure, vital organ perfusion d urine flow.

hen severely hypotensive tients with greatly reduced sys- mic vascular resistance, cardiac and urine output and poor perfusion are given Intropin doses of greater than 20 mcg/kg/min, the blood pressure increases (due to increases in both cardiac output and SVR) while the mild dopaminergic action on the kidney may be somewhat offset by the alpha effect.

Intropin — maintains vital organ perfusion in patients at high risk of shock

Beneficial Intropin effects result from:

- direct increase in blood flow to vital organs, due to dilation of blood vessels in the renal, coronary and mesenteric areas as well as constriction of vasculature of the skin and muscle.
- predictable increase in urine output.
- direct increase of cardiac output, primarily due to increased stroke volume.
- predictable maintenance or increase in blood pressure.

By comparison, other catecholamines (dobutamine, isoproterenol, norepinephrine) while usually favorably affecting cardiac output, may have unpredictable (or even adverse) effects on blood pressure, coronary perfusion or circulation to other vital organs. Increasing the dosage intensifies both the favorable and unfavorable actions of these drugs.

Intropin — recommended for any patient in shock due to:

- myocardial infarction
- trauma
- endotoxic septicemia
- open heart surgery
- renal failure
- congestive heart failure

Intropin dosage forms and concentrations designed for fast, convenient patient care

Please see following page for prescribing information. For furthe information, please contact Medical Services Department of American Critical Care, Division of American Hospital Supply Corporation, 1600 Waukegan Road, McGaw Park, Illinois 60085. Phone 312-473-3000.

INTROPIN®
(dopamine HCl)

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American Critical Care

INTROPIN (dopamine HCl)

5 ml AMPUL and SINGLE-DOSE VIAL
5 ml ADDITIVE SYRINGE (Rap-Add®)
(200 mg and 400 mg concentrations)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally occurring biochemical-catecholamine precursor of norepinephrine. Intropin is a clear, aqueous additive solution for intravenous infusion after dilution.

INDICATIONS: For the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. The physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Note that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce a potentiating effect.

Low Cardiac Output – Increased cardiac output is related to the direct inotropic effect of INTROPIN on the myocardium. Increased cardiac output at low or moderate doses has been associated with either static or decreased systemic vascular resistance (SVR) and appears to be related to a favorable prognosis. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in SVR as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, the drug's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. Administration should be considered as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation. INTROPIN should not be added to any alkaline diluent solution since the drug is inactivated in alkaline solutions. Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage (1/10 the usual starting dose).

Usage in Pregnancy – INTROPIN may be used in pregnant patients when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of INTROPIN for pediatric use has not been established.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site which may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle.

Occlusive Vascular Disease – Patients with a history of occlusive vascular disease (for example, atherosclerosis, arterial embolism, Raynaud's disease, cold injury, diabetic endarteritis, and Buerger's disease) should be closely monitored for any changes in color or temperature of the skin in the extremities.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml of saline solution containing from 5 to 10 mg of Regitine® (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, *phentolamine should be given as soon as possible* after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Because of the theoretical arrhythmogenic potential of these agents and the known increase in cardiac autonomic irritability which may sensitize the myocardium, INTROPIN should be used with EXTREME CAUTION in patients inhaling such anesthetics.

Careful Monitoring Required – As in the case of any adrenergic agent, infusion of INTROPIN should be accompanied by close monitoring of urine flow, cardiac output and blood pressure.

ADVERSE REACTIONS: The most frequent include ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Others reported infrequently are aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

WARNING: This is a potent drug – must be diluted before administration to patient.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since the drug's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED:

– 200 mg (5 ml containing 40 mg dopamine HCl per ml). NDC 0094-0040-05 – Ampul. NDC 0094-0040-06 – Single-dose vial (color coded white). NDC 0094-0040-07 – RAP-ADD® Additive Syringe (color coded white).

– 400 mg (5 ml containing 80 mg dopamine HCl per ml). NDC 0094-0046-06 – Single-dose vial (color coded green). NDC 0094-0046-07 – RAP-ADD® Additive Syringe (color coded green).

CAUTION: Federal law prohibits dispensing without a prescription. Full directions for use should be read before administering or prescribing. November 1980

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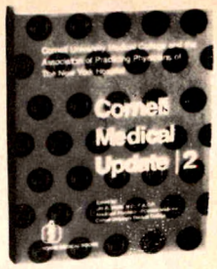
CORNELL MEDICAL UPDATE/2



Edited by LILA A. WALLIS, MD, FACP

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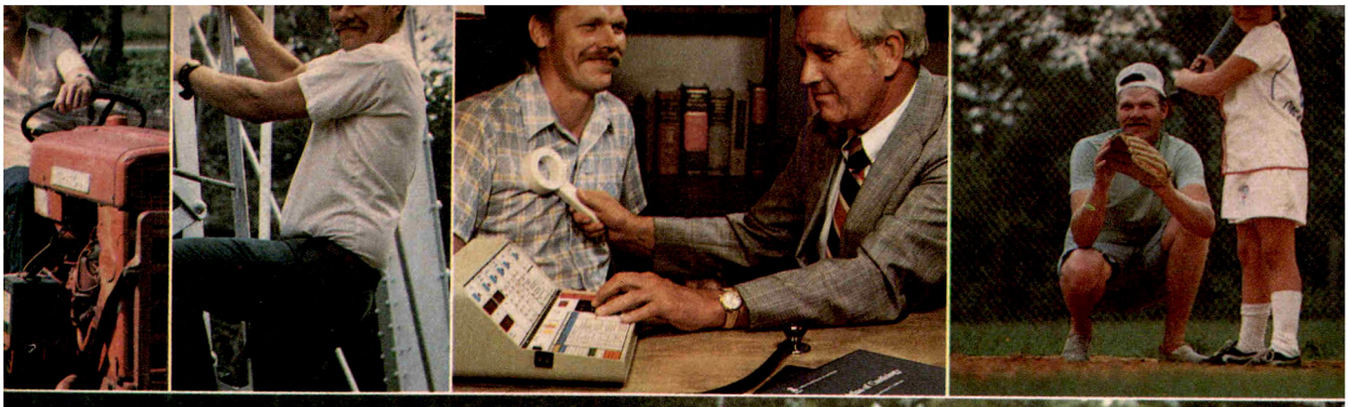

medics Pulse Generators

ATIONS AND CONTRAINDICATIONS

ndications for cardiac pacemaking are increasing as pace- become more sophisticated and as advanced methods for management become more widespread. Generally accepted ons for long-term cardiac pacing include but are not limited ck sinus syndrome; (2) chronic, symptomatic drug-resistant rhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of ac myocardial infarction have not yet been rigorously defined. F to be considered include the location of the myocardial infarc presence or absence of symptoms, ventricular rate, mechanism the arrhythmias, and response to therapy. In general, sympto drug-resistant bradyarrhythmias which impair cardiac output considered indications for pacing in patients with acute myoc infarction, regardless of infarct location.

A CyberLith® Pacemaker helped make these pictures of Wayne Sackett possible.

A LIFETIME OF MASSIVE HEART PROBLEMS IS BEING CONTROLLED WITH A CYBERLITH PACEMAKER, AN AORTIC VALVE, AND SELECTED DRUG THERAPY.

You'd never know by looking at him now, but ten years ago this man collapsed from disabling palpitations while mowing the lawn.

But thanks to an Intermedics CyberLith pacemaker, an aortic valve replacement, and continuing drug therapy, Wayne D. Sackett is more than just back on his feet. He's an active family man, a farmer, and Chief Plant Operator of the Water Department of Deland, Florida.

Taking care of an 11-acre farm is no small task, but Wayne and his wife enjoy making it a family affair with their three children. And the children know that when the chores are all done, it's time for play. Wayne has his favorites—softball, water skiing, fishing, and hunting—and the rest of the family likes to get in on the action.

For Wayne Sackett, as well as his family, the multi-programmable CyberLith pacemaker from Intermedics has proved to be more than a life-saver. In combination with the new valve and the drug therapy, it has been a life-enhancer. And because his physician has him telephonically monitored on a regular basis and can noninvasively make any changes necessary, chances are good that Wayne and his family can go on living as actively as they are now.

Wayne's CyberLith is just one model in the growing Intermedics family of thin, lightweight pacemakers that permit noninvasive programming of stimulating rate, pulse width, sensitivity level, and pacing mode. Because of the CyberLith's long history of reliability—longer than any other programmable multi-parameter pacemaker line—Wayne will probably still be going strong when his five-year-old son is in college.

CyberLith. It could be the pacemaker of choice for your patients.

Intermedics Inc.

P.O. Box 617 Freeport, TX 77541
Toll Free: 800/231-2330

Our business is life.™

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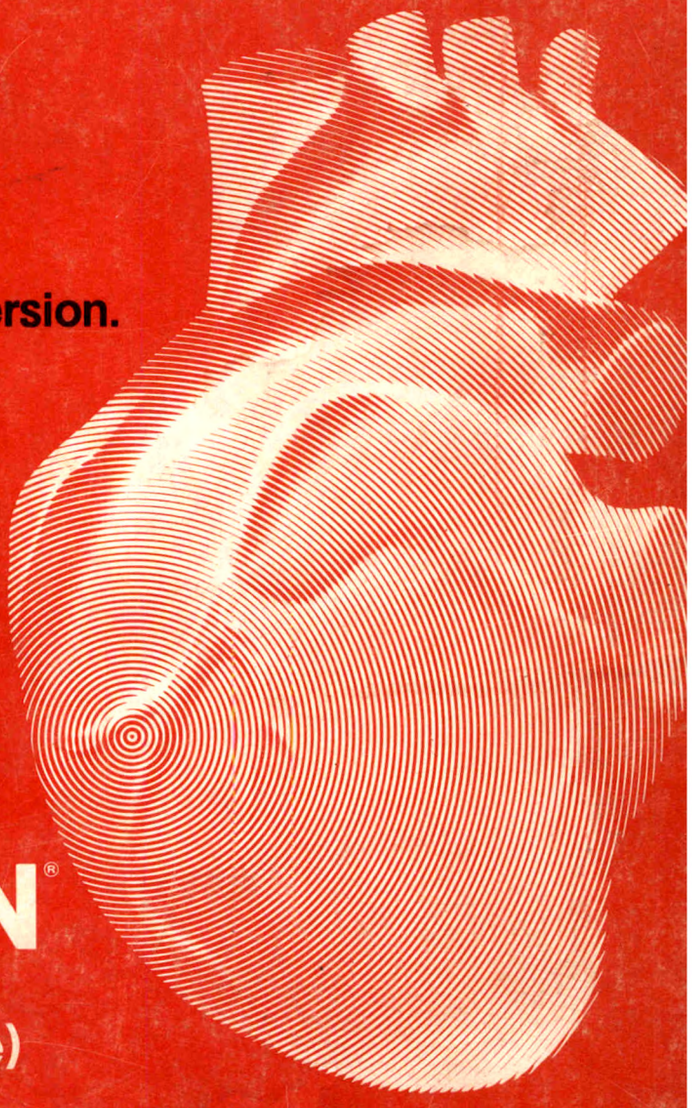
: no known contraindications to the use of pacemakers
l method for control of heart rate. However, body re-
nomena such as local tissue reaction or skin necrosis,
nerve stimulation, embolism, and cardiac tamponade
eported.

ON: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

The Pacekeeper™

For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.



CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion— only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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FEBRUARY 1981

The American Journal of CARDIOLOGY®

OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY

CONVENTION ISSUE

Left Ventricular Function in Aortic Valve Disease

Quantification of Valve Regurgitation With Radionuclide Angiography

Review on Response of the Left Ventricle To Stress

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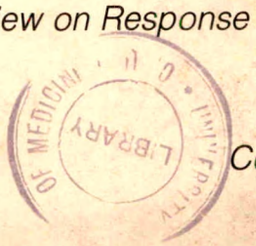


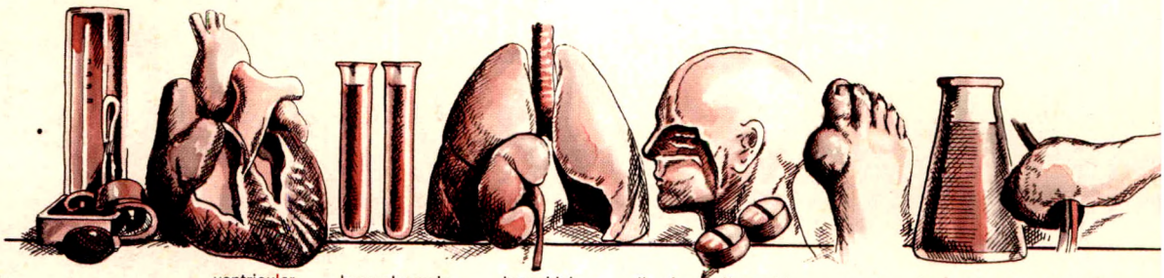
A YORKE MEDICAL JOURNAL

ANSWERS ABOUT ALDOMET® (METHYLDOPA|MSD)

Can an antihypertensive be used in older patients, even those who have certain concurrent diseases?

Special consideration should be given in the selection of an antihypertensive agent for the older patient—especially as to its suitability in the presence of other coexisting problems.

Highly effective and generally well tolerated, ALDOMET can be used in a wide range of hyp tensives, including many older patients with cer concurrent diseases. Its use therefore enhances t possibilities of successful long-term therapy in th older patient.



ALDOMET® offers many other important features:
(METHYLDOPA|MSD)

- Highly effective in all degrees of hypertension.
- Existing cardiac output is usually maintained.
- Renal blood flow is usually maintained.
- May be used in certain cases of complicated hypertension.
- Has documented long-term efficacy.
- Symptomatic postural hypotension is infrequent and the agent is usually well tolerated.

Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease. This may be avoided by lower d ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, or if previou methyldopa therapy has been associated with liv disorders.

It is important to recognize that a positive Coc test, hemolytic anemia, and liver disorders may c with methyldopa therapy. The rare occurrences c hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

For hypertension—

ALDOMET® The most prescribed nondiuretic antihypertensive in the U.S. t
(METHYLDOPA|MSD)

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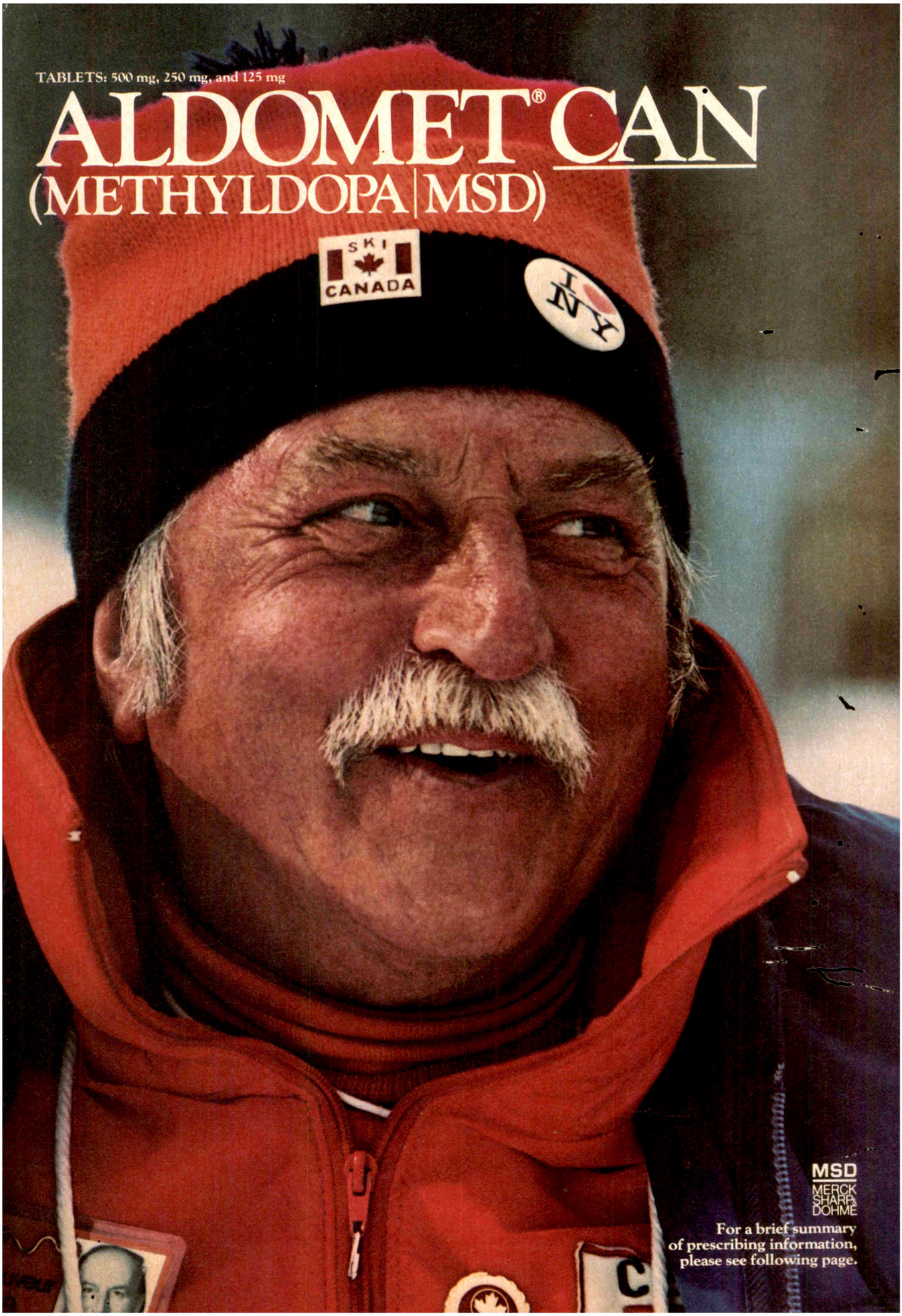
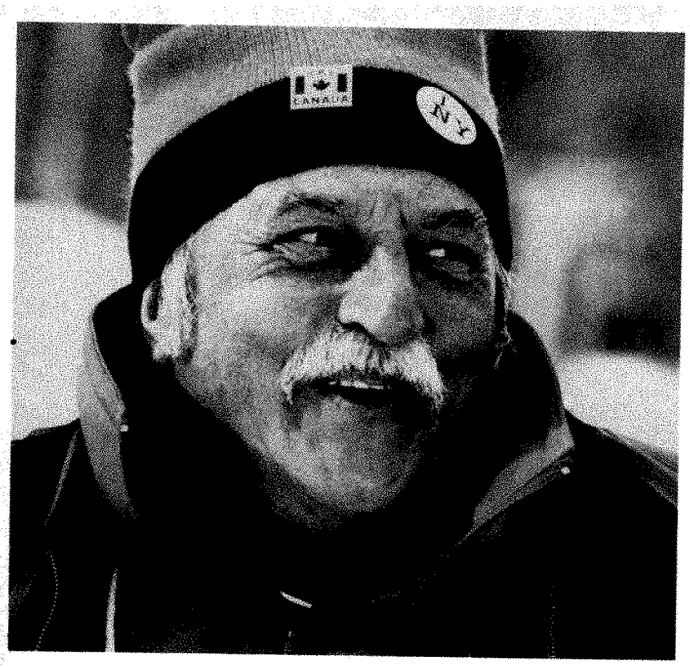

TABLETS: 500 mg, 250 mg, and 125 mg
ALDOMET® CAN
(METHYLDOPA | MSD)
SKI
CANADA
I ♥ NY
MSD
MERCK
SHARP &
DOHME
For a brief summary
of prescribing information,
please see following page.



For hypertension—

ALDOMET (METHYLDOPA | MSD

The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses
anesthetics; hypotension occurring during ane
thesia usually can be controlled with vasopresso
Hypertension has recurred after dialysis in patier
on methyldopa because the drug is removed by tl
procedure.

Adverse Reactions: *Central nervous system:* Sec
tion, headache, asthenia or weakness, usually ea
and transient; dizziness, lightheadedness, sym
toms of cerebrovascular insufficiency, paresthesia
parkinsonism, Bell's palsy, decreased mental acui
involuntary choreoathetotic movements; psyct
disturbances, including nightmares and reversit
mild psychoses or depression.
Cardiovascular: Bradycardia, aggravation of angi
pectoris. Orthostatic hypotension (decrease da
dosage). Edema (and weight gain) usually relieved
use of a diuretic. (Discontinue methyldopa if eden
progresses or signs of heart failure appear.)
Gastrointestinal: Nausea, vomiting, distention, co
stipation, flatus, diarrhea, mild dryness of mout
sore or "black" tongue, pancreatitis, sialadenitis.
Hepatic: Abnormal liver function tests, jaundic
liver disorders.
Hematologic: Positive Coombs test, hemolytic an
mia. Leukopenia, granulocytopenia, thrombocyt
penia. Positive tests for antinuclear antibody, L
cells, and rheumatoid factor.
Allergic: Drug-related fever, lupus-like syndrom
myocarditis.
Other: Nasal stuffiness, rise in BUN, breast enlarg
ment, gynecomastia, lactation, impotence, d
creased libido, dermatologic reactions includin
eczema and lichenoid eruptions, mild arthralgi
myalgia.

Note: Initial adult dosage should be limited t
500 mg daily when given with antihypertensive
other than thiazides. Tolerance may occur, usuall
between second and third months of therap
increased dosage or adding a diuretic frequentl
restores effective control. Patients with impaire
renal function may respond to smaller doses
Syncope in older patients may be related to increase
sensitivity and advanced arteriosclerotic vascula
disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyl
dopa each, in bottles of 100; Tablets, containin
250 mg methyldopa each, in single-unit packages c
100 and bottles of 100 and 1000; Tablets, containin
500 mg methyldopa each, in single-unit packages c
100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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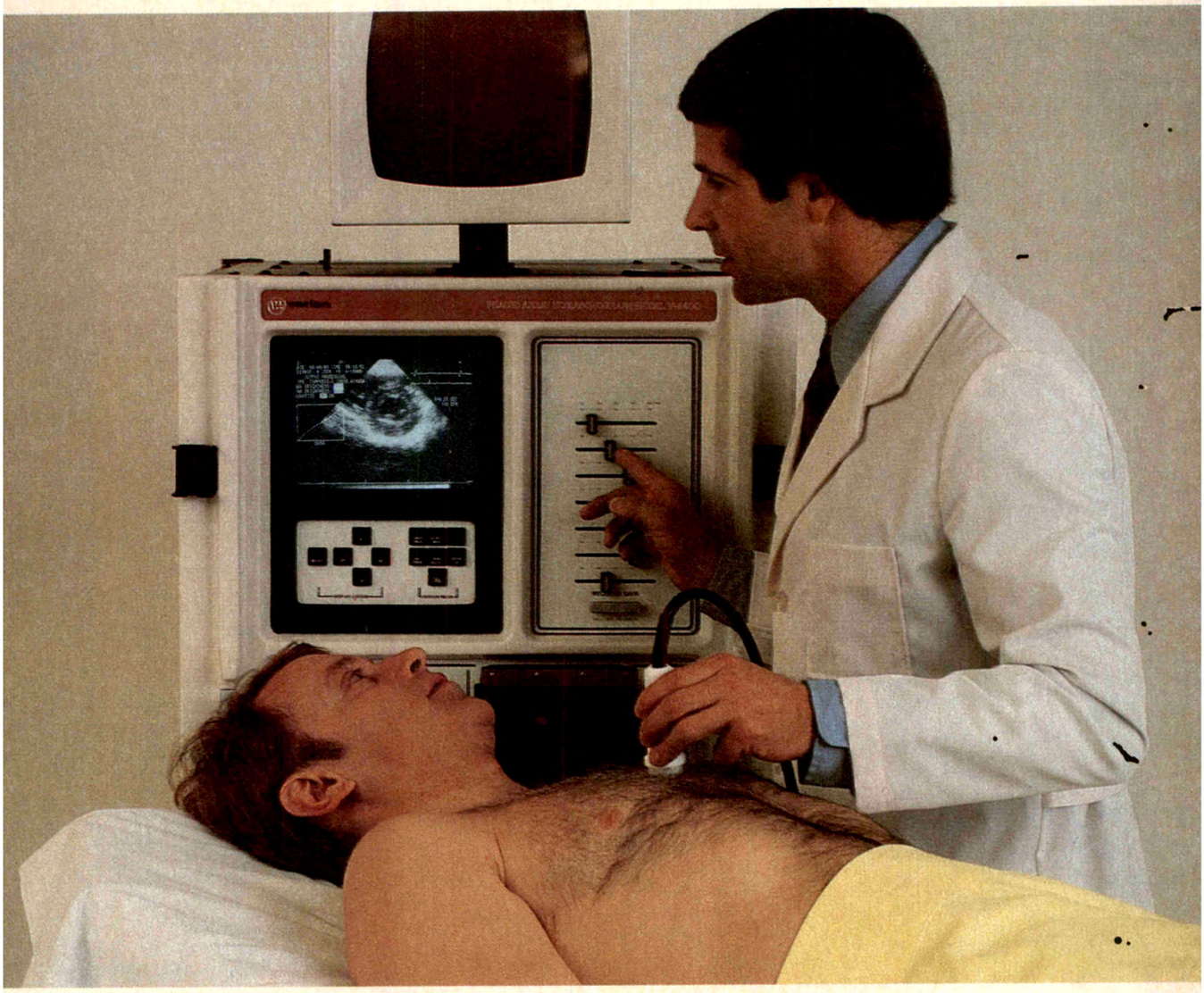

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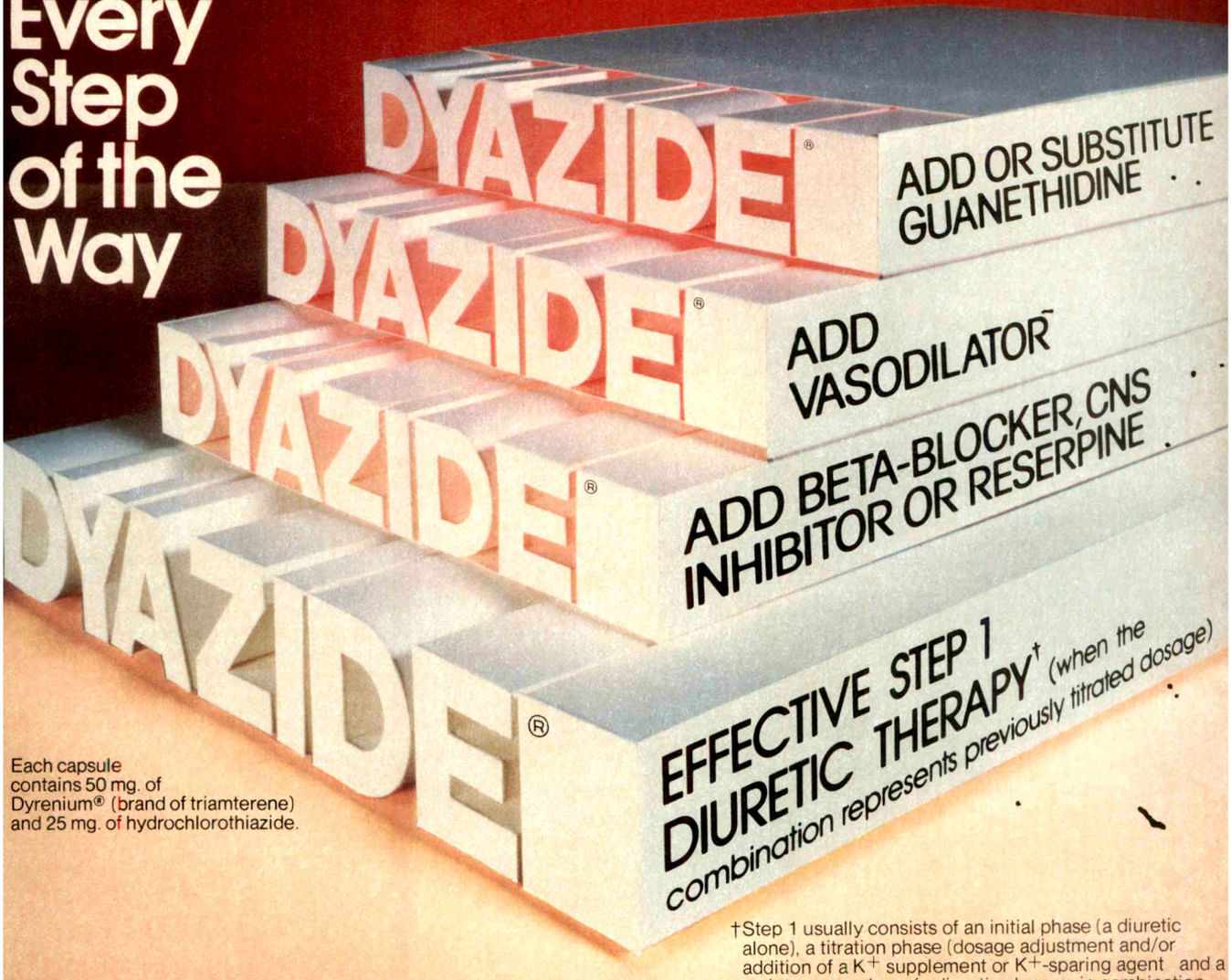

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

Supplied: Bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

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INDICATIONS—Based on a review of this drug by the National Academy of Sciences National Research Council and/or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension. Persantine tablets, 25 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. The incidence of sensitivity is generally low, but frequently seen in patients with aspirin hypersensitivity.

ADVERSE REACTIONS—Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases, higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

Tablets of 25 mg, 50 mg and 75 mg

For complete details, please see the full prescribing information.

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Please see brief summary of prescribing information on adjoining page.

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26790 A

Give your patients the KLORVESS® sparkle

Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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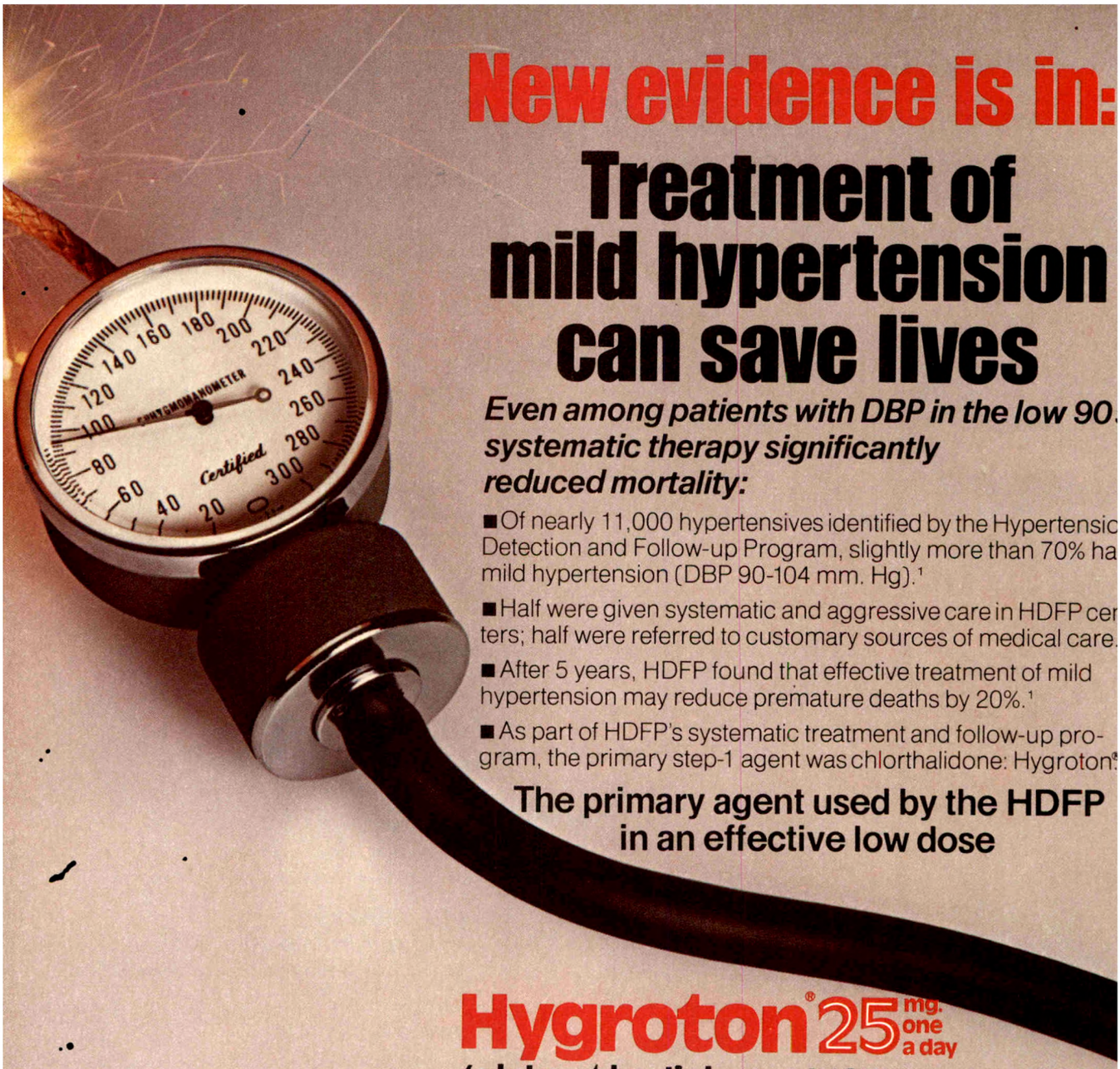

New evidence is in:

Treatment of mild hypertension can save lives

Even among patients with DBP in the low 90. systematic therapy significantly reduced mortality:

- Of nearly 11,000 hypertensives identified by the Hypertensic Detection and Follow-up Program, slightly more than 70% ha mild hypertension (DBP 90-104 mm. Hg).[1]
- Half were given systematic and aggressive care in HDFP cer ters; half were referred to customary sources of medical care.
- After 5 years, HDFP found that effective treatment of mild hypertension may reduce premature deaths by 20%.[1]
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The primary agent used by the HDFP in an effective low dose

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:
1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H.: Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

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The American Journal of CARDIOLOGY®

FEBRUARY 1981 VOLUME 47 NUMBER 2 (IN TWO PARTS)

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193 Left Ventricular Function in Chronic Aortic Regurgitation With Reference to End-Systolic Pressure, Volume and Stress Relations

MARY OSBAKKEN, ALFRED A. BOVE and JAMES F. SPANN

This study of left ventricular contractile and pump function in 12 normal subjects and 21 patients with chronic aortic regurgitation, using conventional methods and the new measure of contractility developed by Sagawa, found the combination of decreased muscle function and increased demands on pump function causes a significant increase in end-diastolic pressure only in patients with heart failure. The contractile and pump functions are reduced when the chronic volume overload progresses to congestive heart failure, but contractile function appears normal and pump function is not significantly reduced in patients whose chronic volume overload has not yet progressed to congestive heart failure. These data also indicate that hypertrophy alone does not decrease myocardial performance. A degree of volume overload and of hypertrophy is associated with normal function, but severe overload with further hypertrophy results in decreased myocardial performance and clinical evidence of congestive heart failure. The data further suggest that patients with aortic regurgitation progress to a symptomatic state when the regurgitant volume becomes greater and the end-diastolic volume and pressure increase.

199 Coronary Sinus Blood Flow at Rest and During Isometric Exercise in Patients With Aortic Valve Disease. Mechanism of Angina Pectoris in Presence of Normal Coronary Arteries

MICHEL E. BERTRAND, JEAN M. LABLANCHE, PIERRE Y. TILMANT, FRANÇOIS P. THIEULEUX, MARC R. DELFORGE and ALAIN G. CARRÉ

These studies in 46 patients with aortic valve disease indicate that coronary blood flow and myocardial uptake of oxygen remain within normal limits in this disorder. Underperfusion of the subendocardial muscle, rather than failure of coronary sinus blood flow to increase, seemed to be a major causative factor in the 18 patients with angina on effort. Special care is needed to protect the myocardium and the subendocardium of these patients during surgical valve replacement. This reserve capacity of vasodilation is unimpaired in these patients as is the ability of the heart to adjust its coronary flow by autoregulation in response to exercise.

206 Congenitally Bicuspid Aortic Valve Causing Severe, Pure Aortic Regurgitation Without Superimposed Infective Endocarditis. Analysis of 13 Patients Requiring Aortic Valve Replacement

WILLIAM C. ROBERTS, ANDREW G. MORROW, CHARLES L. McINTOSH, MICHAEL JONES and STEPHEN E. EPSTEIN

Although not generally recognized as an important factor, the noninfected congenitally bicuspid aortic valve was an important cause of isolated pure aortic regurgitation severe enough to warrant aortic valve replacement in 13 of 189 patients aged 18 to 70 years who had such surgery at the National Heart, Lung, and Blood Institute. In contrast to these 13 patients, only 7 of the 189 patients had pure aortic regurgitation because of infective endocarditis involving a congenitally bicuspid aortic valve.

210 Delayed Pericardial Disease After Radiotherapy

MARK M. APPLEFELD, ROBERT G. SLAWSON, MARY HALL-CRAIGS, DAVID C. GREEN, ROBERT T. SINGLETON and PETER H. WIERNIK

Delayed chronic constrictive pericarditis developed in seven patients 51 to 268 months after they were treated with radiotherapy to the chest for Hodgkin's disease (six patients) and a breast cancer (one patient). Several different pathophysiologic mechanisms may be responsible for such radiation-induced pericardial disease. A surgically produced subxiphoid pericardial window is recommended for patients with cardiac tamponade manifested by dyspnea, hypotension and an echocardiographically confirmed pericardial effusion. Pericardiectomy is recommended if cardiac catheterization confirms constrictive pericarditis in patients with incapacitating dyspnea or marked hepatomegaly (liver more than 16 cm in span). Surgery is not advised solely on the basis of hemodynamic confirmation of constrictive pericarditis or for the presence of recurrent pleural effusions.

214 Hypertrophic Obstructive Cardiomyopathy and Lentiginosis: A Little Known Neural Ectodermal Syndrome

MARTIN G. ST. JOHN SUTTON, ABDUL J. TAJIK, EMILIO R. GIULIANI, HYMIE GORDON and W. P. DANIEL Su

These 11 patients with classic hypertrophic obstructive cardiomyopathy and lentiginosis (a disorder of skin pigmentation that is of neural crest origin) lead these investigators to propose that cardiomyopathic lentiginosis and leopard syndrome are the same entity and that the cardiac lesion common to both is hypertrophic obstructive cardiomyopathy. The presence of lentiginosis, electrocardiographic abnormalities and a systolic murmur should

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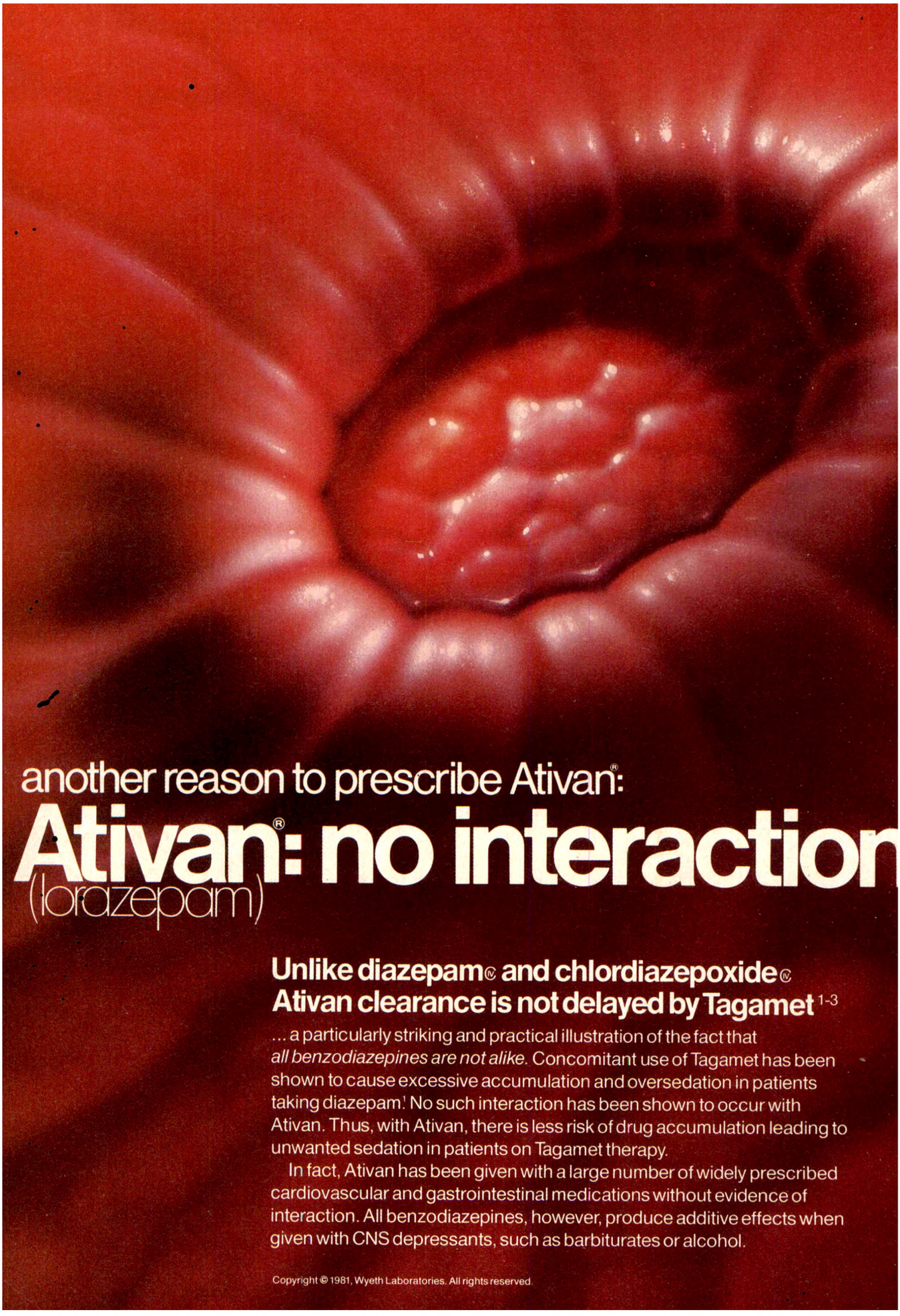

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Other advantages of Ativan (lorazepam):

- Shorter half-life helps avoid excessive accumulation
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References:
1. Klötz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.
2. Desmond PV, Patwardhan RV, Schenker, S, et al: Ann Intern Med *93*:266-268, 1980.
3. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.

*Tagamet (cimetidine) is a registered trademark of Smith Kline & French Laboratories, Division of SmithKline Corporation.

†Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

See important information on following page.

Ativan® (lorazepam) ℞ for Anxiety

Wyeth Laboratories
Philadelphia, PA 19101

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® IV for Anxiety
(lorazepam)

Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

How Supplied: **0.5, 1.0 and 2.0mg tablets.**

Wyeth Laboratories
Philadelphia, PA 19101

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Nitrol®
(nitroglycerin ointment, 2%)

Description: Nitrol® Ointment contains 2% nitroglycerin (glyceryl trinitrate) in a special lanolin-petrolatum base. It is a prompt acting vasodilator, effective in the relief and prevention of anginal attacks.

Action: When the ointment is spread on the skin, the active ingredient (nitroglycerin) is continuously absorbed through the skin into the circulation, thus exerting prolonged vasodilator effect. Nitroglycerin ointment is effective in the control of angina pectoris, regardless of the site of application.

Indications: Prevention and treatment of angina pectoris attacks.

Contraindications: May be contraindicated in patients with marked anemia, increased intraocular pressure or increased intracranial pressure. Should not be employed in patients with known idiosyncrasies to nitrites.

Warning: In terminating treatment of anginal patients, both the dosage and frequency of application must be gradually reduced over a period of 4 to 6 weeks to prevent sudden withdrawal reactions, which are characteristic of all vasodilators in the nitroglycerin class.

Precautions: A hypotensive headache is a sign of overdosage. Occasionally elderly patients may have no untoward symptoms while recumbent but may develop postural hypotension with faintness upon suddenly arising.

Dosage and Administration: For angina pectoris the ointment may be applied every 3 to 4 hours as required. The usual dose is 1 to 2 inches, as squeezed from the tube, although some patients may require as much as 4 or 5 inches. The ointment should be spread in a thin uniform layer on the skin. The optimum dosage is determined by starting with an application of ½ inch of ointment and increasing the dose in ½ inch increments each successive application until headache occurs, then decreasing to the largest dose which does not cause headache. Nitrol Ointment can be applied to any convenient skin area but psychologically, many patients prefer the chest.

Measurement and application of the ointment is easily accomplished with the aid of the specially designed Appli-Ruler™ supplied with the ointment. The ointment can be squeezed onto the graduated area of the Appli-Ruler and conveniently spread over the desired skin area. Keep the tube tightly closed and store at controlled room temperatures.

Caution: Federal law prohibits dispensing without prescription.

Supplied:
30 gram tube NDC 0091-5617-31
60 gram tube NDC 0091-5617-02
30 gram 6-Pack Unit NDC 0091-5617-61
60 gram 6-Pack Unit NDC 0091-5617-62

References:

1. Reichek, N, Goldstein, RE, **et al, Circulation, 50**:Aug. 1974.
2. Meister, SG, Engel, TR, **et al, Br. Heart J., 38**:10, 1976.
3. Taylor, WR, Forrester, JS, **et al, Am. J. Cardiol., 38**:Oct. 1976.
4. Parker, JO, **et al, Am. J. Cardiol., 38**: Aug. 1976.

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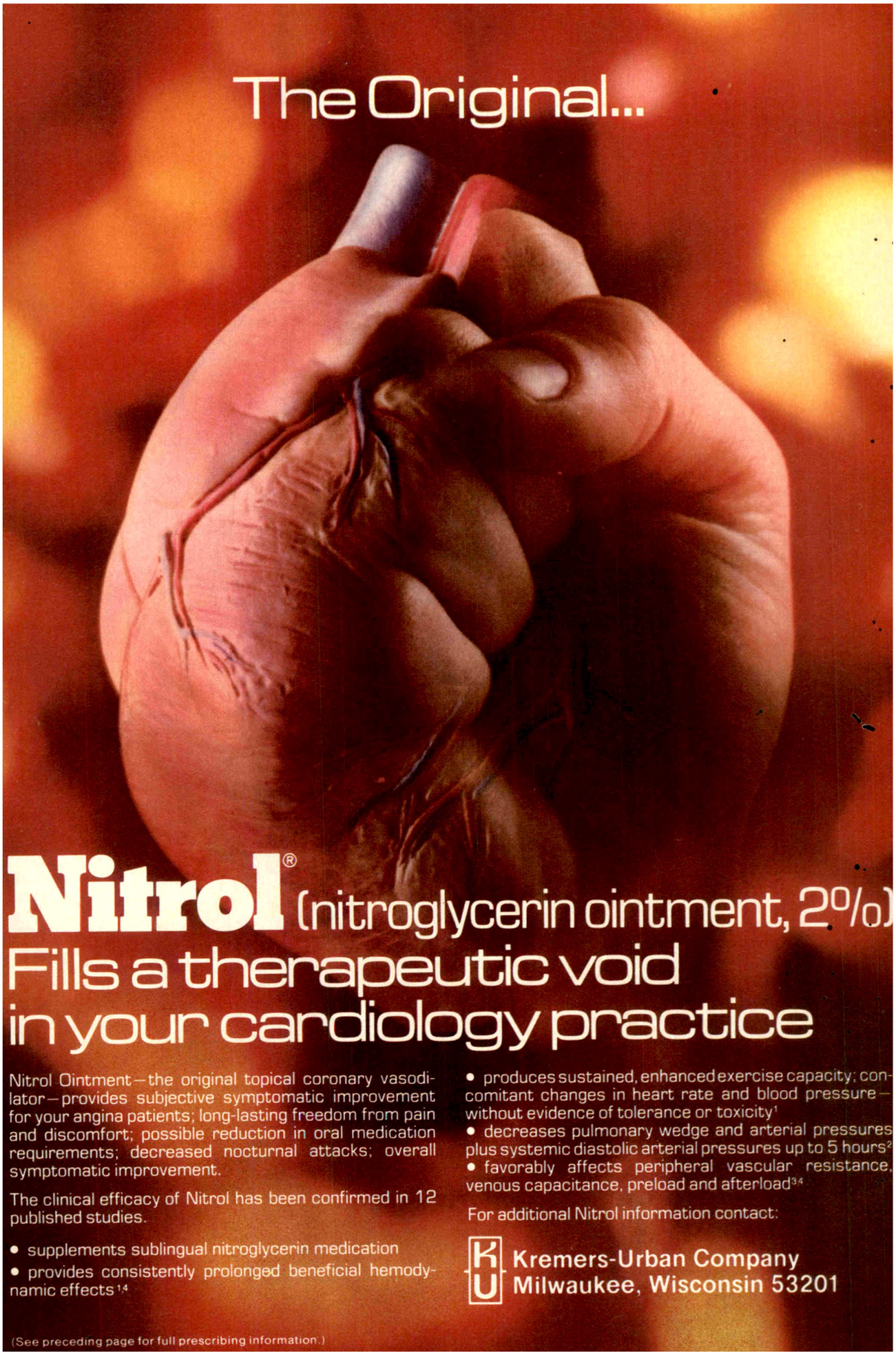

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- produces sustained, enhanced exercise capacity; concomitant changes in heart rate and blood pressure—without evidence of tolerance or toxicity[1]
- decreases pulmonary wedge and arterial pressures plus systemic diastolic arterial pressures up to 5 hours[2]
- favorably affects peripheral vascular resistance, venous capacitance, preload and afterload[3,4]

For additional Nitrol information contact:

Kremers-Urban Company
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(See preceding page for full prescribing information.)

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raise the clinical suspicion of coexistent hypertrophic obstructive cardiomyopathy. Ten o severely symptomatic and 7, each with a left ventricular pressure gradient of more than successful septal myotomy/myectomy with long-term marked symptomatic improvement

218 **History and Physical Examination in Acute Pulmonary Embolism in Patients Without Cardiac or Pulmonary Disease**

PAUL D. STEIN, PARK W. WILLIS III and DAVID L. DeMETS

In this group of 215 patients with acute pulmonary embolism uncomplicated by preexisting disease, dyspnea (84 percent) was the most frequent symptom and tachypnea (85 perce quent sign. Deep venous thrombosis was identified in 41 percent. Dyspnea, tachypnea or c sis was present in 99 percent of patients. Acute pulmonary embolism was rarely identified specific changes of the S-T segment or T wave in the electrocardiogram were found in m the patients with massive or submassive acute pulmonary embolism. A normal electroca mon. The most common abnormalities in the plain chest roentgenogram were pleural Greater reliance on the clinical manifestations will improve the selection of patients for pu and may decrease the reported high frequency of negative pulmonary arteriograms.

224 **Bedside Recognition, Incidence and Clinical Course of Right Ventricular Infarction**

GUILLERMO B. CINTRON, EDGARDO HERNANDEZ, ESTEBAN LINARES and JUAN M

Sixteen of 44 patients with acute inferior wall myocardial infarction had evidence of right Their clinical course was not different from that of others without signs of right ventricu bedside physical diagnosis demonstrating a positive Kussmaul's sign and a right ventricul sound can identify these patients. Right ventricular infarction clinically presents a wide s a rather benign uncomplicated entity to a catastrophic event with atrioventricular block, s Appropriate therapy, including expansion of intravascular volume and use of inotropic ag acute right ventricular infarction and systemic hypoperfusion secondary to inadequate pressure usually produces a satisfactory result.

228 **Unstable Angina Pectoris of New Onset: A Prospective Clinical and Arteriographic S Patients**

MARK F. VICTOR, MARIELL J. LIKOFF, GARY S. MINTZ and WILLIAM LIKOFF

Arteriographic data in 75 patients with unstable angina pectoris of new onset showed ar dence (52 percent) of single vessel coronary artery disease predominantly involving the le coronary arteries, suggesting that these patients constitute a unique subset of patients with patients with single vessel disease did not differ from those with multivessel involvemer factors or clinical presentation. Of the 75 studied, 60 had significant coronary artery dise insignificant coronary disease or entirely normal coronary arteries. Analysis of the 60 pa coronary disease revealed that 52 percent had single, 18 percent had double and 15 per disease and 15 percent had disease of the left main coronary artery either alone or in asso sels.

233 **Prognostic Importance of Anginal Symptoms in Angiographically Defined Coronary A**

PETER F. COHN, PHILLIP HARRIS, WILLIAM H. BARRY, ROBERT A. ROSATI, PAUL CHRISTINE WATERNAUX

Comparison of 44 patients with angiographically defined coronary artery disease and no time of cardiac catheterization with 127 symptomatic patients with similar coronary ana function showed an annual mortality rate of 2.7 percent in the asymptomatic group and 5. with angina. The results of this study suggest that the presence of angina is an important prognosis, but the reasons remain conjectural because the absence of angina neither prec ease nor implies a benign prognosis. The subgroup of asymptomatic patients with three yearly mortality rate of nearly 5 percent. The value of prophylactic medical or surgical treat is unclear at present.

238 **Analysis of Exercise-Induced Changes in R Wave Amplitude in Asymptomatic Men V Electrocardiographic ST-T Changes at Rest**

JOHN YIANNIKAS, JIANIS MARCOMICHELAKIS, PETER TAGGART, BRIAN H. KELLY RICHARD EMANUEL

Symptom-limited treadmill exercise testing of 50 asymptomatic male pilots or allied aviato ing ST-T electrocardiographic changes indistinguishable from those of myocardial ischemi cidence rate of positive results when S-T segment criteria were used. Analysis of changes yielded only two false positive results in men with other heart diseases. Diminished R wave cise, even in the presence of a positive test based on S-T segment criteria, strongly sug coronary artery disease, making coronary angiography unnecessary.

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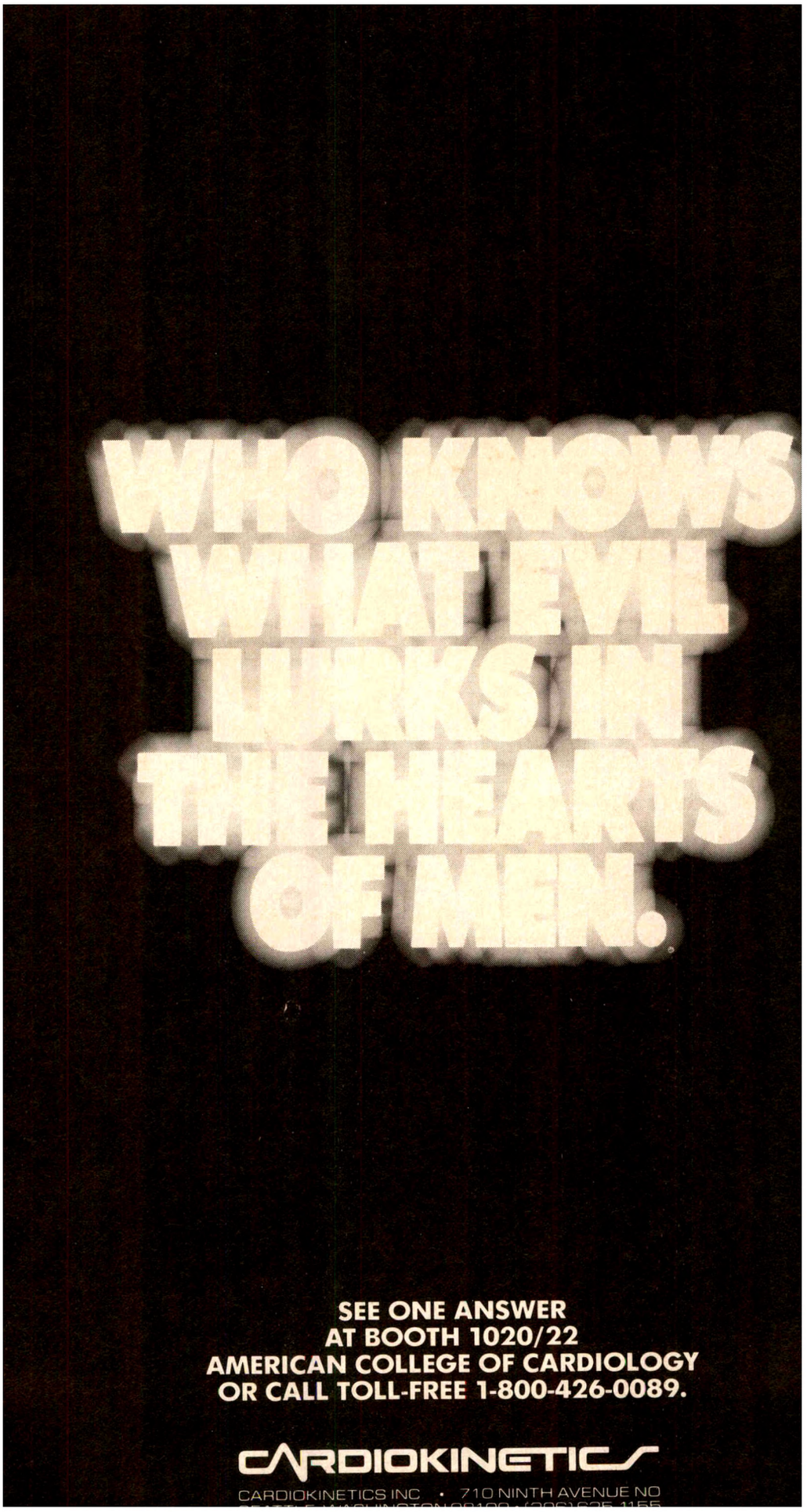
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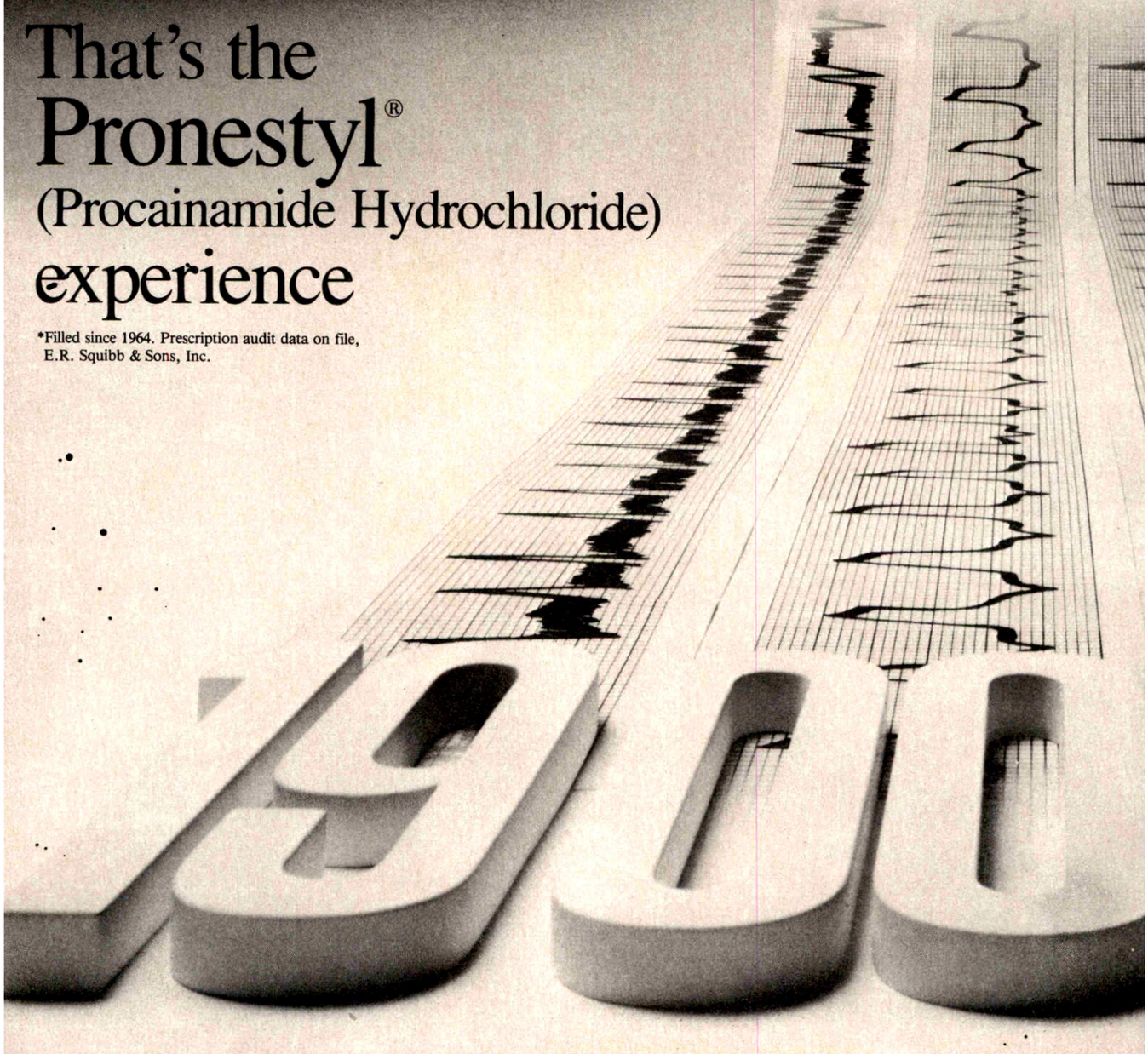

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(Procainamide Hydrochloride)

Please see next page for brief summaries.

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Procainamide Hydrochloride Injection USP

DESCRIPTION: Pronestyl Injection (Procainamide Hydrochloride Injection USP) is a sterile, aqueous solution providing 100 mg or 500 mg procainamide hydrochloride per ml. The 100 mg/ml potency contains 0.9% (w/v) benzyl alcohol and 0.09% sodium bisulfite as preservatives. The 500 mg/ml potency contains 0.1% methylparaben and not more than 0.2% sodium bisulfite as preservatives.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; cross sensitivity to procaine and related drugs must be borne in mind. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of high-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage, procainamide may produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in A-V block, bundle branch block, or severe digitalis intoxication.

Parenteral administration should be monitored electrocardiographically whenever practicable. Parenteral administration should be discontinued at once if electrocardiograms give evidence of impending heart block. This complication should be kept in mind when treating ventricular arrhythmias (especially parenterally) in patients with severe organic heart disease and ventricular tachycardia who may also have complete heart block. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage — principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; discontinue drug in event of rising titer or clinical symptoms of LE. Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Because procainamide is a peripheral vasodilator, I.V. administration may produce transient but at times severe hypotension particularly in conscious patients. I.M. injection is less likely to cause serious falls in blood pressure. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are also more common with I.V. administration.

A syndrome resembling lupus erythematosus has been reported in patients on oral maintenance therapy. Reactions consisting of fever and chills including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in SGOT following single doses of the drug have been reported. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred; therefore, routine blood counts are advisable during maintenance therapy. If soreness of mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

For full prescribing information, consult package insert.

HOW SUPPLIED: Pronestyl Injection (Procainamide Hydrochloride Injection USP) is available in 10 ml vials providing 100 mg procainamide hydrochloride per ml and in 2 ml vials providing 500 mg procainamide hydrochloride per ml.

PRONESTYL® TABLETS
Procainamide Hydrochloride Tablets
PRONESTYL® CAPSULES
Procainamide Hydrochloride Capsules USP

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administratio capsules and veneer-coated tablets providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride. Pronestyl Tablets contain FD&C Yellow No. (tartrazine).

CONTRAINDICATIONS: In patients with myasthenia gravis and where hypersensitivity to procainamide exists; bear in mind cross sensitivity to pr caine and related drugs. Should not be given to patients with complete atr ventricular heart block. Contraindicated in cases of second degree and thi degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damag with atrial fibrillation or flutter, the ventricular rate may increase suddenl the atrial rate is slowed; adequate digitalization reduces but does not aboli this danger. Ventricular tachysystole is particularly hazardous if myocardi damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of th atrium.

Extreme caution is required in attempting to adjust the heart rate when tricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of cond tion and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with seve organic heart disease and ventricular tachycardia that complete heart bloc which may be difficult to diagnose, may be present. Since asystole may res if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the pati reevaluated.

In the presence of both liver and kidney damage, normal dosage may pr duce symptoms of overdosage — principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with ora maintenance procainamide therapy. Common symptoms are polyarthralgi arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion a pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patie on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related continued procainamide therapy (see boxed Warning). Steroid therapy ma effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

Pronestyl Tablets (Procainamide Hydrochloride Tablets) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (includin bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general popu tion is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibri tion are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported in patie on oral maintenance therapy (see Precautions). Reactions consisting of fev and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloac transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenan procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat or gums, unexplained fever or any symptom upper respiratory tract infection. If any of these symptoms should occur a leukocyte counts indicate cellular depression, procainamide therapy should discontinued and appropriate treatment should be instituted immediately. ter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema maculopapular rash have been reported.

For full prescribing information, consult package insert.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Table and Pronestyl Capsules (Procainamide Hydrochloride Capsules USP) providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride are availa in bottles of 100 and Unimatic® cartons of 100. The 250 mg and 500 mg tablets and capsules are also available in bottles of 1000.

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Although aspirin has been shown to inhibit platelet aggregation and to increase epicardial collateral flow by more than 50 percent, pretreatment with platelet-inhibitory doses of aspirin given intravenously failed to reduce the size of the myocardial infarction after ligation of the left anterior descending coronary artery in 34 foxhounds. Aspirin-treated dogs did not differ from control dogs in percent ventricle at risk, percent infarct weight/left ventricle or percent infarct weight/weight of ventricle at risk.

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Studies in 6 dogs and 121 patients demonstrated the value of pulsed Doppler echocardiography as an accurate noninvasive technique for the detection of right-sided valve regurgitation. Increased pressure in the right ventri-

continued on page A32

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Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizzine have occurred in about 10 of 100 patients. Depre sion was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficien usually of the Raynaud type; palpitations and cor gestive heart failure have been reported. See **Co traindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has be reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in abou of 100 patients. Nausea, gastric pain, constipatio flatulence, and heartburn have been reported in 100 or less.

Allergic: Pruritus has occurred in less than 1 of 1 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety adverse effects not listed above have been reported with other beta-adrenergic blocking agent and should be considered potential adverse effe of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time an place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respir tory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopresso should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added t diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum ef fect of any given dosage level will be apparent aft one week of therapy. Usual maintenance dosage i approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg p day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients especially when lower dosages are used, will exp rience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughou the day. If control is not adequate, a larger dose, three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room tem perature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

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Dispense in tight, light-resistant container (USP).

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For complete details, including description, clinic pharmacology and overdosage, please see full prescribing information.

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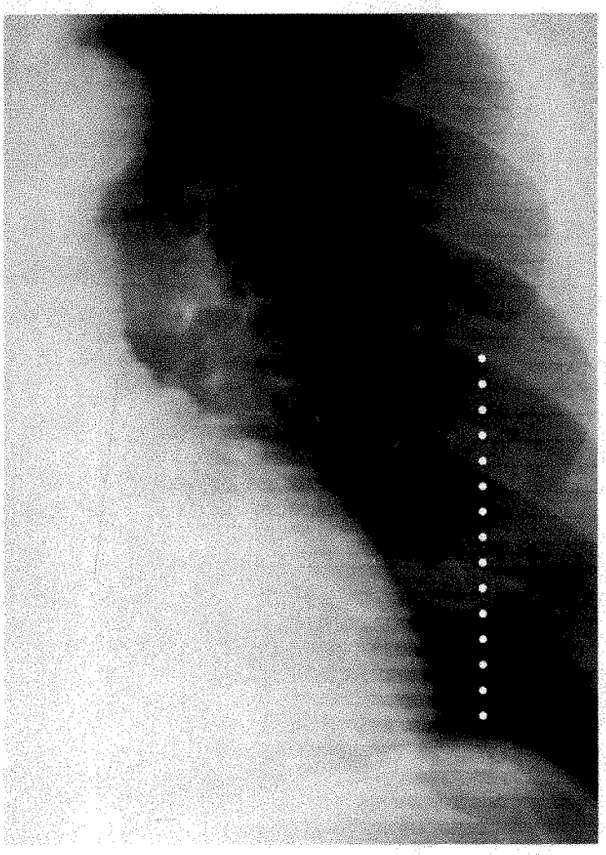

IRS x-ray shows an asynergistic contraction. Systolic ›s are marked in this image with white dots, clearly trating normal motion in the basal segment, hypokine- n the lateral wall and paradoxical motion in the apex.

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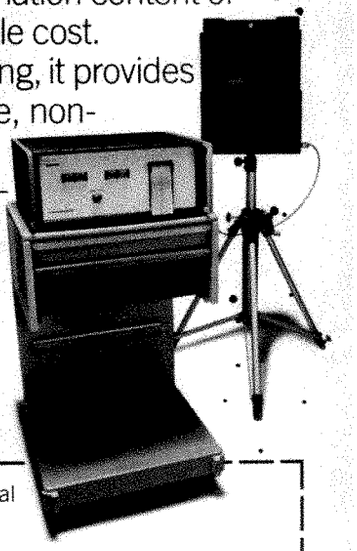

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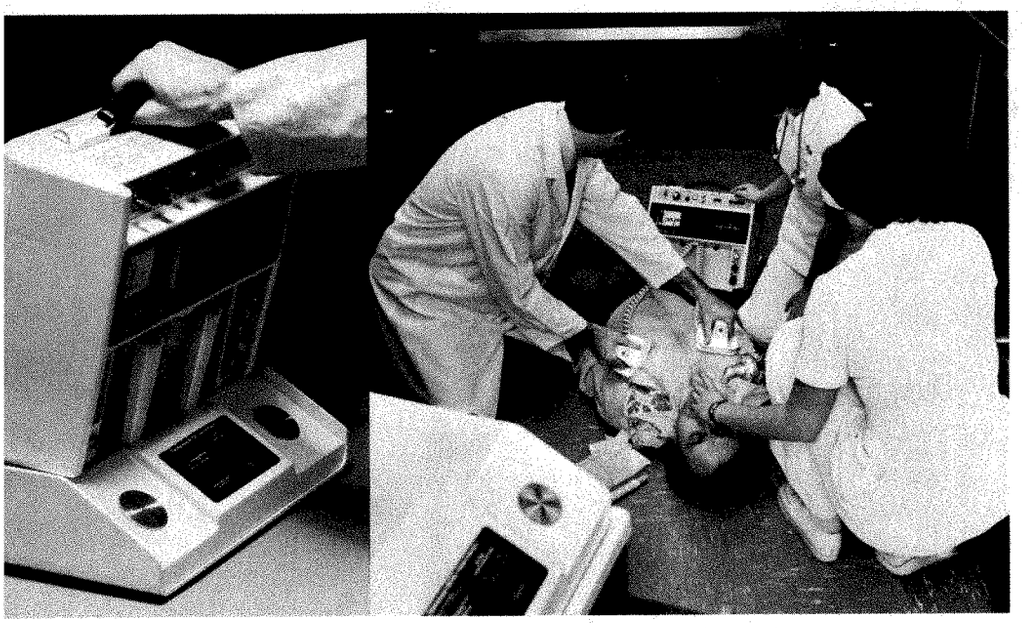

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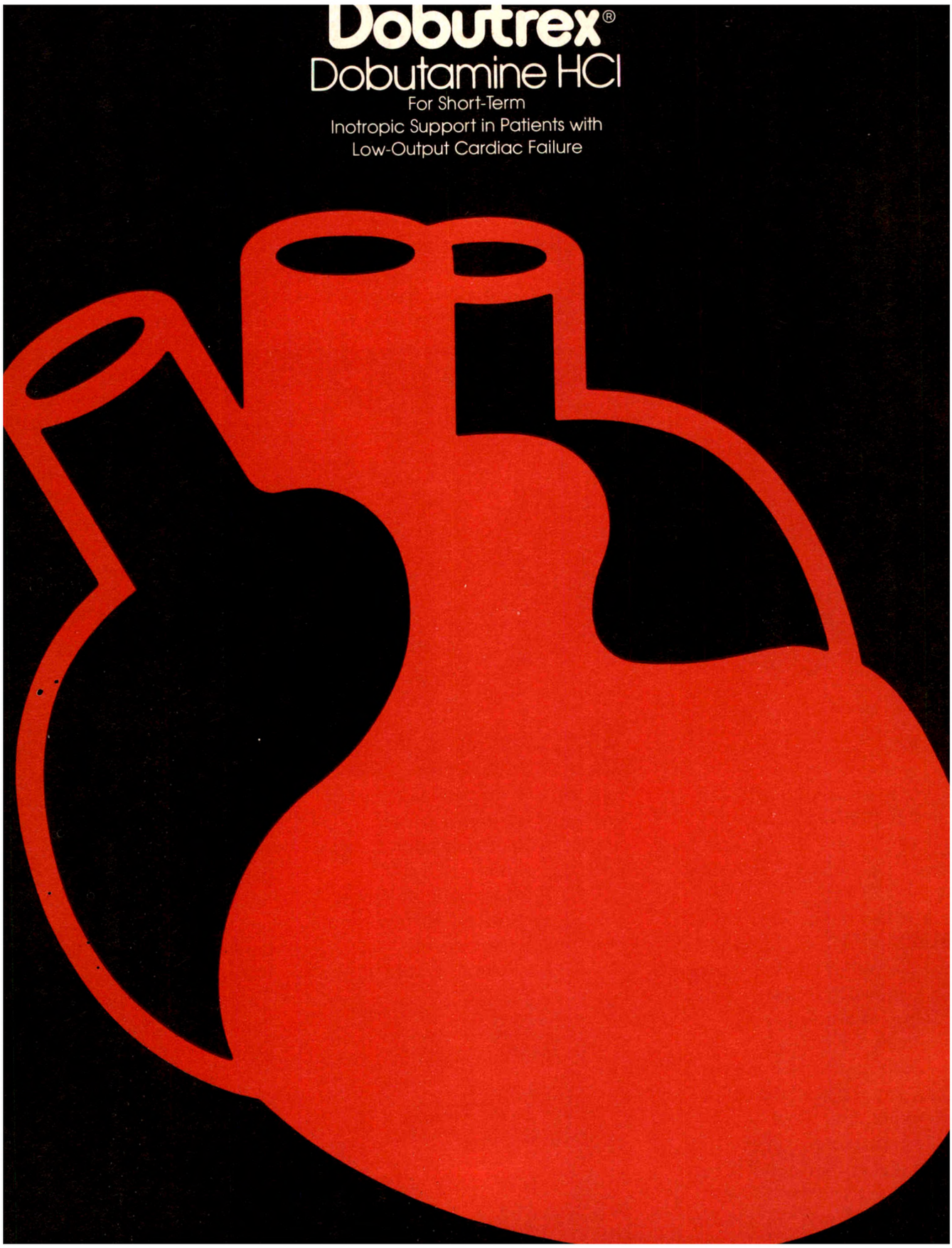

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tications and Usage: Dobutrex® (do- tamine hydrochloride, Lilly) is indicated en parenteral therapy is necessary for in- opic support in the short-term treatment adults with cardiac decompensation due depressed contractility resulting either m organic heart disease or from cardiac gical procedures.
n patients who have atrial fibrillation with oid ventricular response, a digitalis prep- ation should be used prior to instituting rapy with Dobutrex.

ntraindication: Dobutrex is contraindi- ted in patients with idiopathic hyper- phic subaortic stenosis.

rnings: 1. *Increase in Heart Rate or Blood essure*—Dobutrex may cause a marked rease in heart rate or blood pressure, ecially systolic pressure. Approximately 10 rcent of patients in clinical studies have d rate increases of 30 beats/minute or re, and about 7.5 percent have had a -mm Hg or greater increase in systolic essure. Reduction of dosage usually re- rses these effects promptly. Because butamine facilitates atrioventricular con- ction, patients with atrial fibrillation are at of developing rapid ventricular response. tients with preexisting hypertension ap- ar to face an increased risk of developing exaggerated pressor response.
2. *Ectopic Activity*—Dobutrex may precipi- e or exacerbate ventricular ectopic ac- ty, but it rarely has caused ventricular chycardia.

cautions: 1. During the administration of butrex, as with any adrenergic agent, ECG d blood pressure should be continuously nitored. In addition, pulmonary wedge essure and cardiac output should be nitored whenever possible to aid in the fe and effective infusion of Dobutrex.
2. Hypovolemia should be corrected with itable volume expanders before treatment th Dobutrex is instituted.
3. Animal studies indicate that Dobutrex ay be ineffective if the patient has recently ceived a beta-blocking drug. In such a se, the peripheral vascular resistance may crease.
4. No improvement may be observed in e presence of marked mechanical struction, such as severe valvular aortic enosis.
Usage Following Acute Myocardial farction—Clinical experience with Dobu- ex following myocardial infarction has een insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250,500, and 1000 mcg/ml

Drug Delivery Rate	Infusion Delivery Rate			
	250 mcg/ml*	500 mcg/ml†	1000 mcg/ml‡	
(mcg/kg/min)	(ml/kg/min)	(ml/kg/min)	(ml/kg/min)	
2.5	0.01	0.005	0.0025	
5	0.02	0.01	0.005	
7.5	0.03	0.015	0.0075	
10	0.04	0.02	0.01	
12.5	0.05	0.025	0.0125	
15	0.06	0.03	0.015	

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

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cle or pulmonary arteries was present in 90 and 86 percent of patients with Doppler evidence of tricuspid or pulmonary insufficiency, respectively, suggesting a causal relation between high pressure states and mild degrees of right-sided valve regurgitation as detected by pulsed Doppler recording. Because of its high incidence rate (87 percent) and association with pulmonary hypertension (87 percent) pulsed Doppler detection of tricuspid or pulmonary insufficiency, or both (in the absence of pulmonary stenosis) was found superior to M mode electrocardiographic measurements and clinical auscultation in the prediction of pulmonary hypertension.

287 **Quantification of Valve Regurgitation by Radionuclide Angiography Before and After Valve Replacement Surgery**

JOANN URQUHART, RANDOLPH E. PATTERSON, MILTON PACKER, STANLEY J. GOLDSMITH, STEVEN F. HOROWITZ, ROBERT LITWAK and RICHARD GORLIN

This study validates the use of the stroke index ratio determined with radionuclide angiocardiography as a noninvasive estimate of the magnitude of valve regurgitation in 20 patients with aortic or mitral valve disease, or both. This ratio was higher in patients with aortic and mitral regurgitation than in a control group of 10 patients without regurgitation. After aortic and mitral valve replacement in 18 patients, the stroke index ratio decreased from 4.03 ± 1.46 to 1.38 ± 0.23, not significantly different from that in patients without regurgitation. These data establish a linear relation between the index and quantitative calculations of the regurgitant factor in man. A stroke ratio index of greater than 1.62 indicates significant valve regurgitation preoperatively and suggests residual regurgitation postoperatively. These data substantiate the value of radionuclide angiography as a noninvasive method of detecting and quantifying the magnitude of left-sided valve regurgitation by comparing left ventricular and right ventricular systolic and diastolic counts.

292 **Radionuclide Regurgitant Index: Value and Limitations**

WILFRED LAM, DAN PAVEL, ERNEST BYROM, AMJAD SHEIKH, DAVID BEST and KENNETH ROSEN

In this study of 100 patients with left-sided valve regurgitation graded angiographically, the radionuclide regurgitant index (left ventricular/right ventricular stroke counts obtained from gated equilibrium study) was 2.9 to 1.5 in 51 patients, 1.6 to 2.4 in 23 and 2.5 to 12.0 in 26. The index significantly differed between patients with no regurgitation and each group with regurgitation and between groups with regurgitation separated by two or more grades of angiographic regurgitation. A discordant (or spurious) regurgitant index was found in 12 patients with a markedly reduced left ventricular ejection fraction or mitral valve prolapse with frequent ventricular extrasystoles. Recognizing this potential source of error should make the radionuclide regurgitant index more useful for assessing the presence and severity of left-sided valve regurgitation.

PEDIATRIC CARDIOLOGY

299 **Treatment of d-Transposition of the Great Arteries: Management of Hypoxemia After Balloon Atrial Septostomy**

CATHERINE G. HENRY, DAVID GOLDRING, ALEXIS F. HARTMAN, CLARENCE S. WELDON and ARNOLD W. STRAUSS

In a group of 43 patients with d-transposition of the great arteries who underwent Rashkind balloon atrial septostomy at the time of initial catheterization, 88 percent survived to the time of intraatrial baffle repair between 6 and 12 months and 72 percent were long-term survivors. Prostaglandin E_1 infusion proved life-saving and provided sufficient palliation in patients with persistent hypoxemia and acidosis after balloon atrial septostomy. In these patients, discontinuation of prostaglandin E_1 infusion resulted in return of oxygen saturation to preinfusion levels but no further metabolic acidosis. As a consequence of their experiences these investigators provided the following guidelines for early management of patients with transposition of the great vessels: (1) balloon atrial septostomy and conservative medical management for all patients without acidosis regardless of oxygen saturation following Rashkind septostomy, (2) prostaglandin E_1 infusion, and (3) early Senning or Mustard intraatrial baffle repair.

307 **Results of Intraventricular Baffle Procedure for Ventricular Septal Defect and Double Outlet Right Ventricle or d-Transposition of the Great Arteries**

PAUL PITLICK, JAMES FRENCH, DIANA GUTHANER, NORMAN SHUMWAY and DAVID BAUM

In this group of 30 patients with ventricular septal defect and d-transposition of the great arteries or double outlet right ventricle who underwent placement of an intraventricular baffle to achieve physiologic correction there was an overall 22 percent early mortality rate and an additional 20 percent mortality rate primarily related to problems of conduction disturbances and pulmonary vascular obstructive disease. These problems have not occurred in patients operated on since 1974. In this series small patient size was the major factor related to early mortality. The risk of surgical death was 7 times higher in patients who weighed less than 10 kg than in patients who weighed more than 10 kg. All 17 current survivors are asymptomatic, and many show significant weight gain. In spite of the problems associated with the intraventricular baffle procedure, the investigators believe that the overall improvement outweighs the risks of the procedure and present their guidelines for surgical intervention.

continued on page A35

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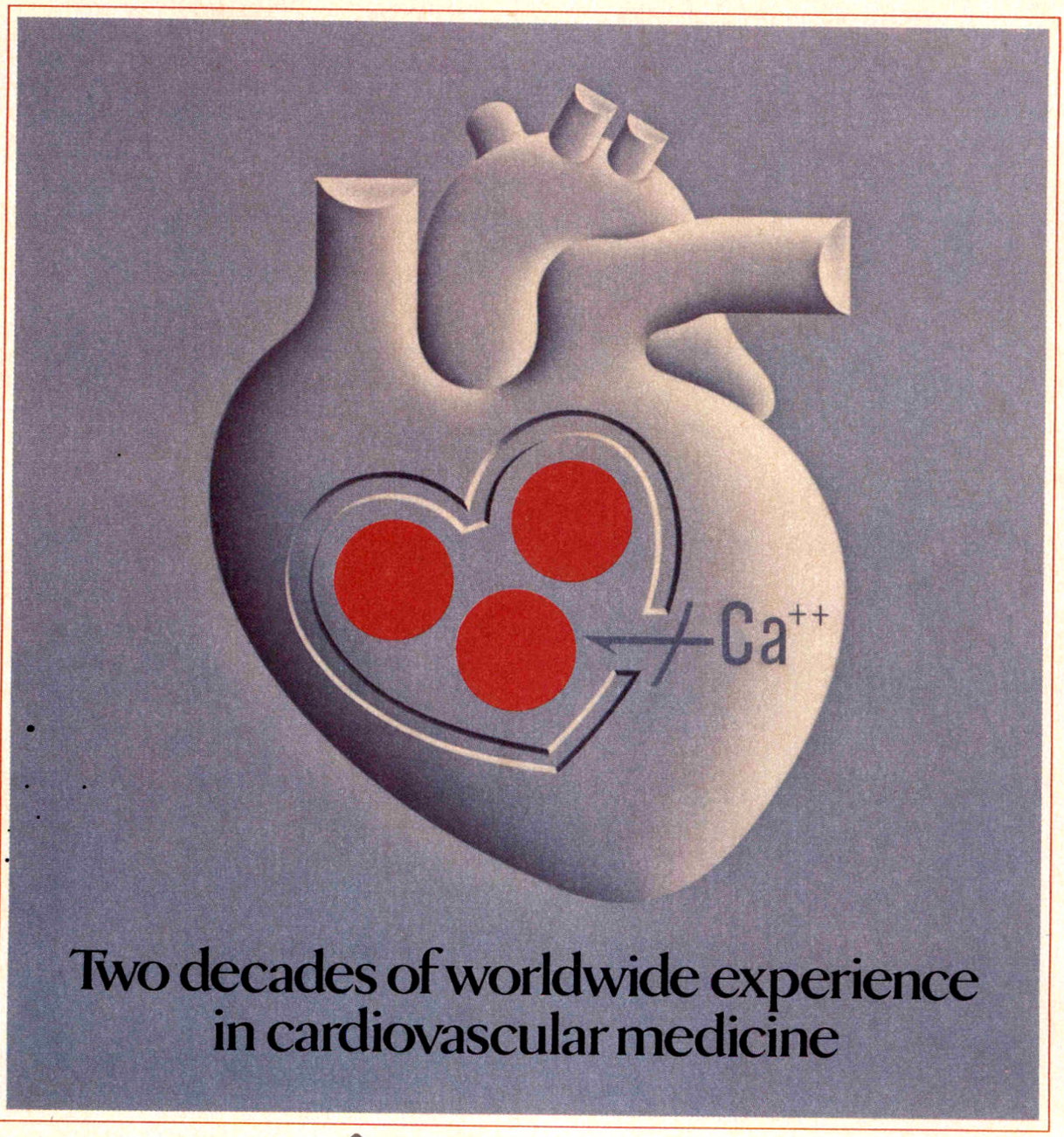

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CONTENTS

315 **Idiopathic Recurrent Sustained Ventricular Tachycardia in Children and Adolescents**

VICTORIA L. VETTER, MARK E. JOSEPHSON and LEONARD N. HOROWITZ

Electrophysiologic studies of recurrent sustained ventricular tachycardia in 7 pediatric patients confirm that tachycardia was more frequently due to an automatic than to a reentrant mechanism, originated more often in the right ventricle and was infrequently associated with structural heart disease. One patient had a coronary arterial abnormality of undetermined significance; six had normal angiographic and hemodynamic studies. Ventricular tachycardia was infrequently initiated and terminated by programmed electrical stimulation. These differences in the frequency of the reentrant mechanism of ventricular tachycardia in children and adults as well as the differences in the anatomic substrate necessitate differences in evaluation and therapy of ventricular arrhythmias in these age groups.

323 **Clinical Course of Cardiovascular Involvement in the Mucocutaneous Lymph Node Syndrome. Relation Between Clinical Signs of Carditis and Development of Coronary Arterial Aneurysm**

SATOSHI HIRAISHI, KIMIO YASHIRO, KOKI OGUCHI, SHOICHI KUSANO, KATSUMI ISHII and KEIJI NAKAZAWA

Data collected in 79 Japanese children with the mucocutaneous lymph node syndrome revealed the presence of myocarditis in 50.6 percent during stages I and II and of one or more coronary aneurysms in 11 patients primarily in stage II. Regression of the aneurysm was noted in five of these patients later during stages III, IV and V. Regression of aneurysms demonstrated angiographically does not imply complete recovery of the coronary artery because it may result from a reduction of the internal lumen due to some pathologic mechanism. The occurrence of coronary aneurysm did not correlate with the presence of clinical signs of carditis. The frequency of carditis was the same in patients with and without aneurysm. This study therefore shows no distinct relation between coronary aneurysm formation and clinical carditis.

REPORTS ON HYPERTENSION

331 **Platelet Function in Hypertension and Effect of Therapy**

JAWAHAR MEHTA and PAULETTE MEHTA

Evaluation of platelet function in 10 hypertensive and 11 normal subjects suggests that enhanced platelet activation in primary hypertension may be associated with increased vascular resistance. The levels of plasma beta thromboglobulin (the secretory product of platelets released by their alpha granules during the release reaction) were significantly increased in certain patients with hypertension. After blood pressure was controlled with lofexidine, plasma beta thromboglobulin levels decreased in 9 of the 10 hypertensive patients but increased in 1 with no change in blood pressure. Further studies are needed to determine whether such inhibition of platelet activation with platelet-suppressive agents ameliorates any of the clinical sequelae in hypertensive patients.

335 **Clinical Correlates in Hypertensive Patients With Left Ventricular Hypertrophy Diagnosed With Echocardiography**

ANDRÉ COHEN, ARTHUR D. HAGAN, JOHN WATKINS, JOHN MITAS, MARIO SCHVARTZMAN, ALBERTO MAZZOLENI, IRVING M. COHEN, S. E. WARREN, and W. V. R. VIEWEG with the technical assistance of WILLIAM ELIAS and LINDA SAMTOY

M mode and two dimensional echocardiography in 73 hypertensive patients revealed left ventricular hypertrophy (using a posterior wall thickness of 12 mm as the criterion) in 37 patients (51 percent); 29 had concentric hypertrophy and 8 had disproportionate septal thickening. Electrocardiography proved insensitive in identifying left ventricular hypertrophy in these patients. The presence of increased left ventricular mass was associated with a greater incidence of other target organ disease, resulting in stroke, hypertensive retinopathy, impaired renal function and elevated serum creatinine. Ten percent had decreased left ventricular performance evidenced by fractional shortening of less than 31 percent and mild diffuse hypokinesia on two dimensional studies.

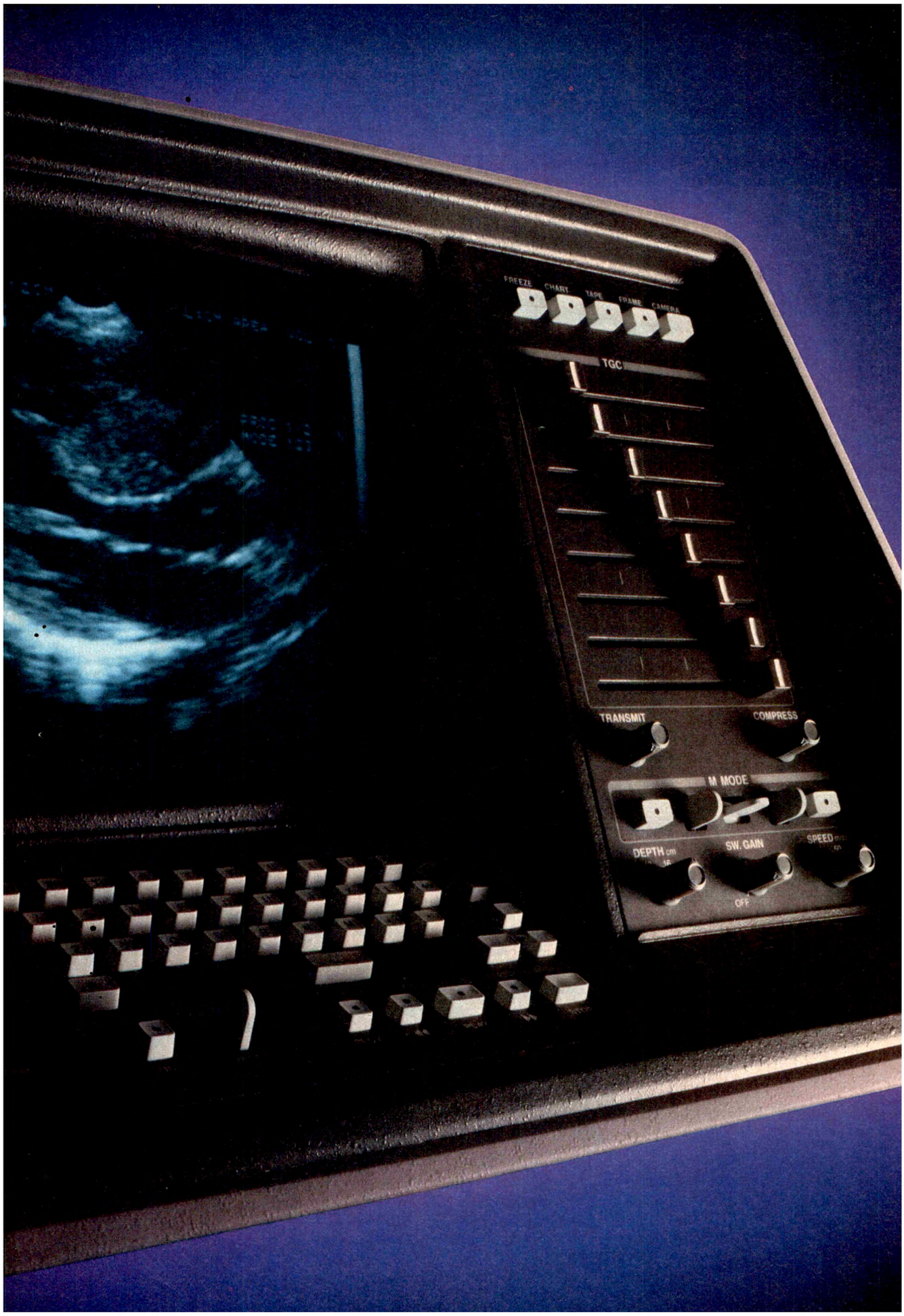
REVIEWS

343 **Clinicopathologic Correlates of Acute Ischemic Heart Disease Syndromes**

L. MAXIMILIAN BUJA and JAMES T. WILLERSON

This clinicopathologic review of 100 recent myocardial infarct in 83 patients demonstrates that acute ischemic heart disease has no constant relation with the severity of chronic atherosclerosis. Myocardial necrosis, usually limited to subendocardial involvement, commonly occurs in the absence of acute coronary occlusion. Acute coronary thrombosis frequently determines the extent and distribution of an evolving infarct. Coronary thrombus formation does not depend on a generalized impairment or coronary perfusion either before or after the onset of infarction. The frequent association of coronary thrombosis with plaque erosion, rupture and hemorrhage strongly suggests that the key initiating event in thrombus formation occurs in the coronary artery. The clinical

continued on page A38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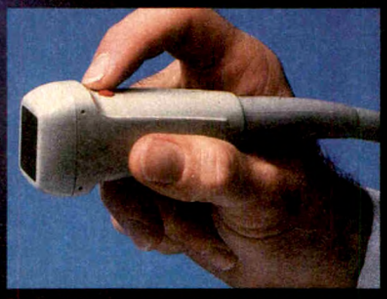

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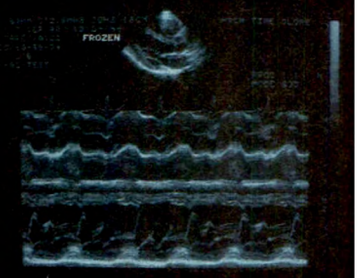

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onset of infarction was followed by severe cardiac pump failure or congestive heart failure in 63.9 percent of infarcts associated with and 41 percent of infarcts not associated with recent occlusion. Acute events can be precipitated by factors that increase myocardial oxygen demand or reduce cardiac or coronary reserve. Additional factors of potential importance include platelet alterations, imbalance in the prostacyclin-thromboxane A_2 system and altered adrenergic function and the probable influence of these factors on induction of coronary arterial spasm.

357 **Response of the Left Ventricle to Stress: Effects of Exercise, Atrial Pacing, Afterload Stress and Drugs**

ROBERT SLUTSKY

This review summarizes the response of left ventricular performance and size to atrial pacing, afterload stress and various forms of exercise in normal subjects and subjects with coronary heart disease. Most testing methods include aerobic and anaerobic exercise as well as the infusion of agents that alter preload, afterload and inotropic states. Many exercise-induced abnormalities in left ventricular size and function of patients with coronary artery disease may be reversed by pretreating the patient with sublingual nitroglycerin or nitroglycerin paste before the exercise study. Atrial pacing reduces cardiac size in normal subjects with little change in ejection fraction, cardiac output or peripheral vascular resistance. Velocity indexes increase. In patients with ischemic heart disease ventricular volume declines, ejection fraction decreases or remains unchanged and new wall motion abnormalities may appear. Cardiac output does not change because stroke volume declines in proportion to the increase in heart rate. In both normal subjects and subjects with heart disease isoproterenol infusions reduce systemic vascular resistance, increase cardiac output and index and increase ejection fraction with a reduction in both end-diastolic and end-systolic volumes.

DIAGNOSTIC SHELF

365 **Echocardiographic Mimicry of Pericardial Effusion**

PATRICIA C. COME, MARILYN F. RILEY and NICHOLAS J. FORTUIN

Abnormal echocardiographic patterns mimicking pericardial effusions were revealed in four patients in whom anatomic structure, a coronary artery to coronary sinus fistula (one case) and metastatic tumors to the pericardium (three cases) produced posterior or anterior spaces compatible with pericardial fluid. Since an improper echocardiographic diagnosis of pericardial effusion may result in unwarranted pericardiocentesis or more aggressive surgical procedures, appropriate attention must be paid to recognition of technical artifacts and other anatomic conditions that mat simulate pericardial effusion. Two dimensional echocardiography may enhance the diagnosis.

371 **"Supernormal" Phase of Atrioventricular Conduction With Concealed Capture Beats. Significance of Odd Number of P Waves Between Capture Beats**

ALAN LINDSAY and LEO SCHAMROTH

These two case reports are of special interest because they reflect for the first time concealed supernormal atrioventricular (A-V) nodal penetration and confirm a mathematical hypothesis previously propounded to explain this particular manifestation of A-V nodal supernormality on the basis of differential horizontal refractoriness.

EDITORIALS

375 **Continued Gains in Hypertension**

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the drawbacks of using retrospective evidence and call for the formation of a multi-center, double-blind, randomized study on the use of anticoagulants in acute myocardial infarction.

Screening the high risk group The risk of DVT (deep vein thrombosis) is particularly great among certain patient groups:

- patients with left ventricular failure
- patients in shock
- patients with arrhythmias
- older patients
- obese patients
- patients with varicose veins
- patients with previous myocardial infarction or thromboembolism

Screening techniques Diagnosis of DVT by physical examination may miss a significant number of clinically silent thrombi. There are, however, additional technological tools to help the clinician define more accurately the incidence of deep vein thrombosis. Among these are:

iodine-125 fibrinogen scanning—radioactively tagged fibrinogen is incorporated into actively forming thrombi and is detected on external sensors. This method is accurate for popliteal and calf vein thrombi, but not for iliofemoral thrombi.[2]

Phlebogram showing occlusion in deep vein of the upper calf.

venography—radiographic evidence of DVT is seen as a constant filling defect in venous projections, abrupt termination of a column of contrast material at a constant site, nonfilling of the deep veins, and presence of flow in collateral veins.[4]

ultrasound—Doppler ultrasound scanning can provide a fast, convenient, inexpensive reading of deep venous obstruction. This technique is potentially the most versatile and accurate method available. However, it demands considerable operator experience to insure maximal accuracy.[5]

impedance plethysmography—this technique results from the observation that blood volume changes in the calf produced by inflation or deflation of a thigh cuff produce variations in electrical resistance (impedance). Such changes are reduced in patients with thrombosis of the popliteal or more proximal veins.[4]

Patient compliance through education Providing the anticoagulated patient with information about his altered physical state and motivating him to comply with the therapeutic regimen constitute one of the most important aspects of health care.[6]

To determine the best way of imparting necessary information about anticoagulation to patients, a test was devised. One group of patients was given a brochure detailing the need for the medication and the importance of following the doctor's instructions. A second group of patients was given a programmed instruction booklet which was quite comprehensive in its teaching content, which included the action of warfarin, the purpose of prothrombin times, how to figure dosage from tablet strengths, possible complications and steps to take to control them.

When tested for learning and retention, the patients in the programmed instruction group scored significantly higher than the group given brochures only. In an area of medicine that relies so heavily on patient compliance, this report could be important in determining how medical information is communicated to the patient.[6]

The bottom line A postmortem study[7] underlines the importance of thrombosis in myocardial infarction. In this study of 173 patients with recurrent myocardial infarction, coronary occlusion due to thrombosis occurred in 54% of cases. Recent occlusive coronary thrombosis was 4 times less frequent in patients who received adequate anticoagulation (mean prothrombin level was 29 ± 5%).

And as one authority states:

"Rational use of anticoagulant therapy in the setting of acute myocardial infarction may save more than 8,000 lives a year in this country. Full advantage should be taken of this therapeutic opportunity."[2]

For prescribing information on COUMADIN® (crystalline warfarin sodium) tablets, including information relating to side effects and contraindications, please see full prescribing information on the following page.

References:

1. Gazes PC, Gaddy JE: Bedside management of acute myocardial infarction. *Am Heart J 97*(6):782-96, Jun 1979. 2. Frishman WI, Ribner HS: Anticoagulation in myocardial infarction: Modern approach to an old problem. *Am J Cardiol 43*(6):1207-13, Jun 1979. 3. Szklo M, *et al:* Additional data favoring use of anticoagulant therapy in myocardial infarction. *JAMA 242*(12):1261-64, Sept 21, 1979. 4. Hirsch J: Venous thrombosis, in *Anticoagulation: Principles and Practice,* Temple University School of Medicine and Endo Laboratories 5. Thrombosis, a symposium. *Contemp Surg 14*:80, 1979. 6. Rankin MA: Programmed instruction as a patient teaching tool: A study of myocardial infarction patients receiving warfarin. *Heart Lung 8*(3):511-16, May-Jun 1979. 7. Barrillon A, Kusmierek J, Gerbaux A: Occlusive coronary thrombosis and oral anticoagulants. *Thromb Haemost 41*(1):255-64, Feb 28, 1979.

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crystalline warfarin sodium, U.S.P.*

TABLETS

DESCRIPTION COUMADIN (crystalline warfarin sodium), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN (crystalline warfarin sodium) usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN (crystalline warfarin sodium) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system; (2)eye; (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts; (2)cerebrovascular hemorrhage; (3)aneurysms—cerebral, dissecting aorta; (4)pericarditis and pericardial effusions; (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis, or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN (crystalline warfarin sodium) are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation—Coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; bromelains; chloral hydrate†; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; COUMADIN (crystalline warfarin sodium) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements; ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; pyrazolones; phenylbutazone; phenyramidol; phenytoin; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; sulindac; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

*Present as crystalline sodium warfarin isopropanol clathrate.

†Increased and decreased prothrombin time responses have been reported.

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ENDO-924C Printed in U.S.A. Nov. 1980

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN (crystalline warfarin sodium) underdosage; diet high in vitamin K; diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN (crystalline warfarin sodium) patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X is not accelerated by the administration of a loading dose.

Maintenance—Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy—The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery—The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin—Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe.

It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium, USP). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide, accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

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Update on Oral Anticoagulation

TREATING MYOCARDIAL INFARCTION AND REDUCING THE THREAT OF THROMBOEMBOLISM

Each year in this country approximately one million people suffer acute myocardial infarctions. Rapid emergency treatment in coronary care units has been credited with reducing by up to one third the mortality among patients hospitalized with acute attacks.[1]

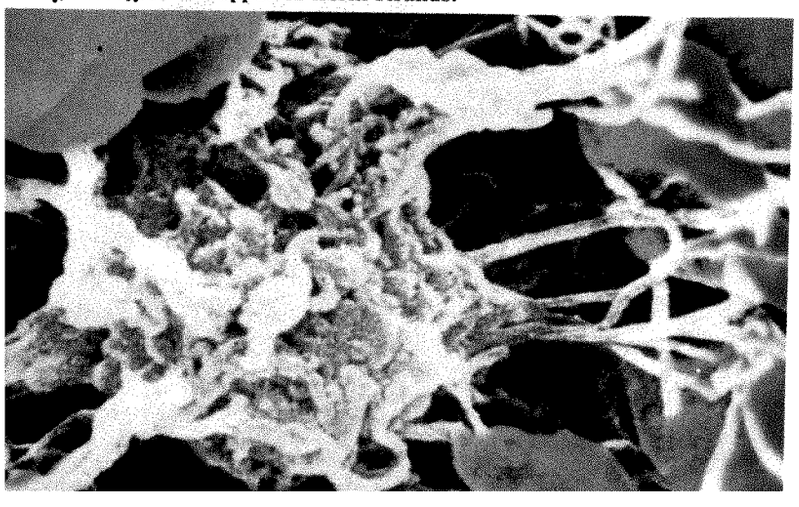
Thrombosis—incidence in myocardial infarction Following the damage to the heart itself, thromboembolism is perhaps the most serious sequel to myocardial infarction.

A study has demonstrated that there is a 39% incidence of calf vein thrombosis during the acute phase of myocardial infarction.[1]

Speed saves lives It has been reported that more than half the thrombi destined to occur in the calf veins form within 72 hours of myocardial infarction, and three-fourths form within the first week. Therefore, a number of investigators have recommended that antithrombotic measures should begin upon admission to the hospital and be effective almost immediately.[2]

Oral anticoagulants have a clinical value It has also been stated that the use of anticoagulants may reduce the frequency of calf vein thrombosis from 22 to 6.5%. The use of anticoagulants is subject to differing opinions regarding improved survival. A number of authorities recommend the use of anticoagulants in *all* patients who have no specific contraindications during the period of hospitalization.[1]

Scanning electron micrograph of 'Red' thrombus, formed by erythrocytes entrapped in fibrin strands.



One team of investigators in M.I. recommends providing full-dose warfarin while the patient is in the hospital and for several days afterward—

if the patient has had prior infarcts or thromboembolism
if the area of infarction is large
if complications (such as CHF or hypotension require prolonged bed rest.

But, if post myocardial infarction syndrome (Dressler's syndrome) develops, anticoagulants should be discontinued, as pericardial hemorrhage even cardiac tamponade may develop.[1]

Objectives and benefits of anticoagulation The use of anticoagulants in the acute phase of myocardial infarction has these potential advantages:[2]

prevention of deep vein thrombosis
reduction of embolization from cardiac mural thrombi
prophylaxis against extension of myocardial necrosis or long-term recurrence of infarction
reduction of overall mortality

If anticoagulants can inhibit the formation of deep vein thrombi, then the incidence of pulmonary embolism might be diminished—and pulmonary embolism has been estimated as a threat to life in 5,000 of the 500,000 myocardial infarction patients who are admitted to hospitals in this country each year.

A look at survival One retrospective study of the use of anticoagulants in M.I. evaluated the survival of 1,307 patients from 20 hospitals in a large metropolitan community. The diagnosis of M.I. was based on predefined criteria, which included typical chest pain, serial ECG's, enzyme elevations, and autopsy findings.

Among anticoagulated patients, the adjusted in-hospital case-fatality rate was 18%. For patients who did not receive this treatment, the fatality rate was 31%. For survivors followed for as long as ten years, patients who had been anticoagulated still fared better than those not so treated.[3]

The authors of this study recognize

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ECHOCARDIOGRAPHY, 3rd ed.

By HARVEY FEIGENBAUM, M.D., *Indiana University School of Medicine, Indianapolis.* This book by Doctor Harvey Feigenbaum has been the principle authoritative book in the field since publication of the first edition. This new Third Edition maintains and improves on that status. It represents a definitive, thorough discussion of instrumentation, technical aspects of application, and future trends by a pioneer in the field. Major coverage of two-dimensional echocardiography is featured. Discussion of this relatively new technique represents a major part of the text and is the principle reason for the increase in size. It is now completely reorganized to reflect current change in the status of echocardiography as an integral part of clinical cardiology. Several hundred new illustrations add to the usefulness of the book, and permit it to function as an atlas. The extensive list of up to date references enhance its value as a superior reference source. *580 pp. (7 × 10), 732 illus. (2 in color), 1981, $35.00.*

AMBULATORY ELECTROCARDIOGRAPHY: Including Holter Recording Technology

By HAROLD L. KENNEDY, M.D., *Johns Hopkins Hospital and the University of Maryland, Baltimore, Maryland.* This long-needed monograph describes the state of the art of ambulatory electrocardiography and Holter technology, and serves as a textbook with regards to its technique, interpretation and clinical indications. The content is directed specifically to both physicians and cardiovascular technical personnel interested in performing and interpreting ambulatory electrocardiographic examinations. Doctor Kennedy is well aware of emerging Holter technologies which show promise of becoming important in the future, and has made every effort to produce a very up-to-the-minute book for a rapidly changing field. No other book deals so completely and comprehensively with the practical aspects of this technology, its data analysis and interpretation, and the ambulatory electrocardiography literature. *About 300 pp. (7¼ × 10¼), 204 illus., 5 tables, 1981, Ready Soon.*

CARDIAC CATHETERIZATION AND ANGIOGRAPHY, 2nd ed.

Edited and with contributions by WILLIAM GROSSMAN, M.D., *Peter Bent Brigham Hospital, Boston, Massachusetts.* (*24 Contributors*). Taking a highly pragmatic approach, this new edition provides a completely up-to-date summary of the major techniques currently employed in cardiac catheterization and angiography. Review of previous edition: "Magnificent . . . the best current book on cardiac catheterization."—*The American Journal of Cardiology. 427 pp. (7 × 10), illus., 1980, $34.50.*

Plan now to examine our many new books at the American College of Cardiology meeting in San Francisco, California, March 16–19, 1981. We will be at Booth 2121.

CARDIAC REHABILITATION, ADULT FITNESS, AND EXERCISE TESTING

By PHILIP K. WILSON, Ed.D., *La Crosse Exercise Program, University of Wisconsin, La Crosse;* PAUL S. FARDY, Ph.D., *St. Catherine Hospital, East Chicago, Indiana; and* VICTOR F. FROELICHER, M.D., *University of California, San Diego.* This book provides extensive coverage of all aspects of cardiac rehabilitation and adult fitness programs, with additional emphasis placed upon theory, procedures, and techniques of exercise testing. *462 pp., illus., 1981, $29.50.*

PROGRESS IN CARDIOLOGY. 9

Edited by PAUL N. YU, M.D., *University of Rochester School of Medicine and Dentistry, Rochester, New York; and* JOHN F. GOODWIN, M.D., *Royal Postgraduate Medical School, London, England.* (*22 Contributors*). Chapters discuss management of the late phase of acute myocardial infarction; detection of postinfarction ventricular aneurysm using cross-sectional echocardiography and radionuclide ventriculography; the current status of computed tomographic (CT) scanning of the heart; etc. *193 pp. (7 × 10), illus., 1980, $15.00.*

GUIDELINES FOR GRADED EXERCISE TESTING AND EXERCISE PRESCRIPTION, 2nd ed.

Edited by the AMERICAN COLLEGE OF SPORTS MEDICINE, *Madison, Wisconsin. Prepared by the Preventive and Rehabilitative Programs Committee.* The new Second Edition sets forth a rationale for the establishment of effective graded exercise testing, exercise prescription, and exercise programs for asymptomatic subjects, as well as patients with cardiovascular and respiratory disease. *151 pp., tables, paperback, 1980, $6.50.*

CARDIAC EMERGENCY CARE, 2nd ed.

Edited and with contributions by EDWARD K. CHUNG, M.D., *Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania.* (*22 Contributors*). Busy physicians will appreciate the new format and quick and easy access to information provided in this Second Edition. Three new chapters dealing with sick sinus syndrome and brady-tachyarrhythmia syndrome, nursing aspects of cardiac emergency care, and radiological diagnosis in cardiopulmonary emergencies are included. *475 pp., illus., tables, 1980, $25.00.*

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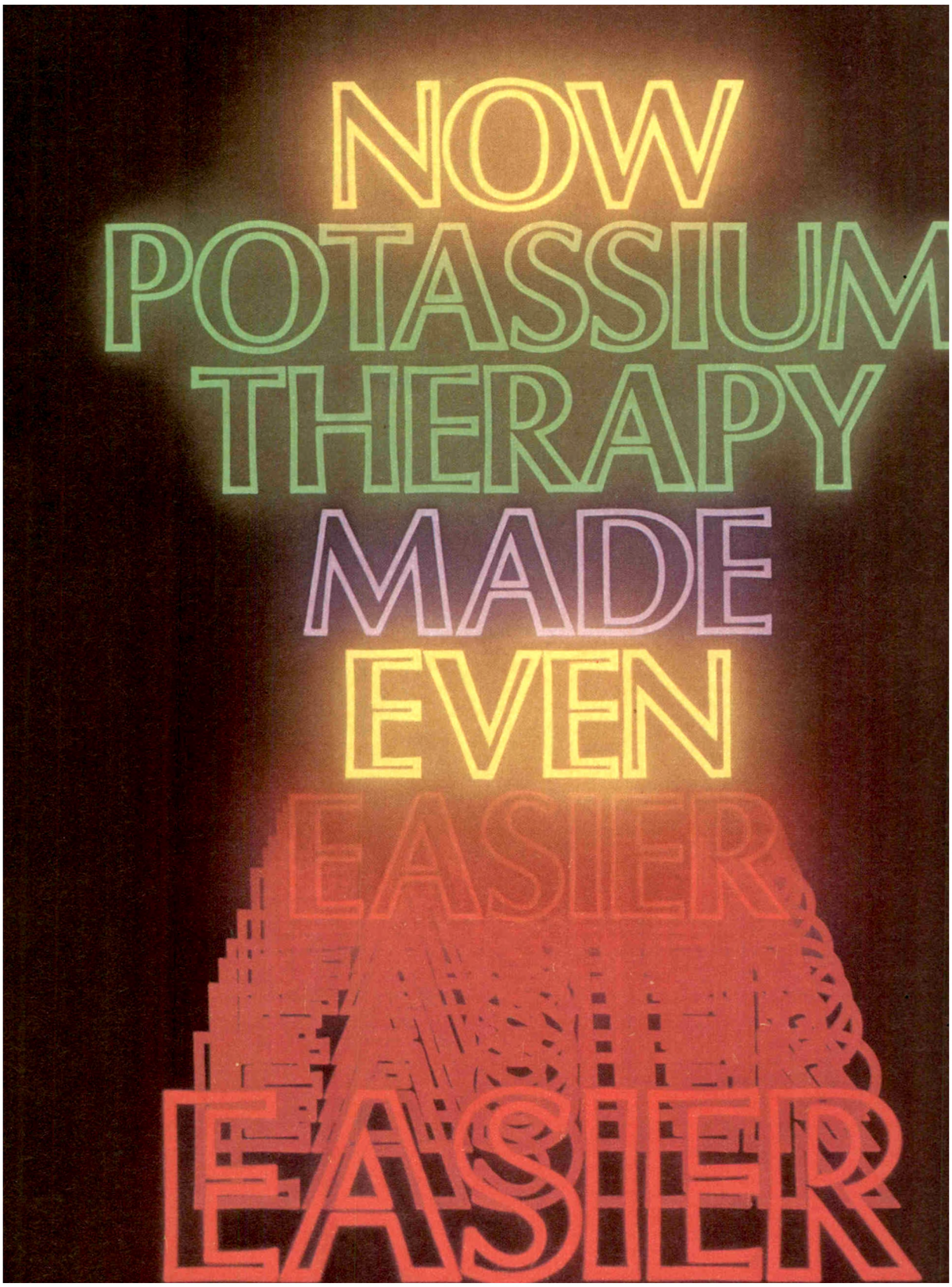
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Brief Summary

Description: Kaon Cl™-10 mEq is a sugar coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq potassium chloride) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

Indications: BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUIDS OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon Cl™-10 mEq (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon Cl-10 mEq should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-15 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

Caution: Federal law prohibits dispensing without prescription.

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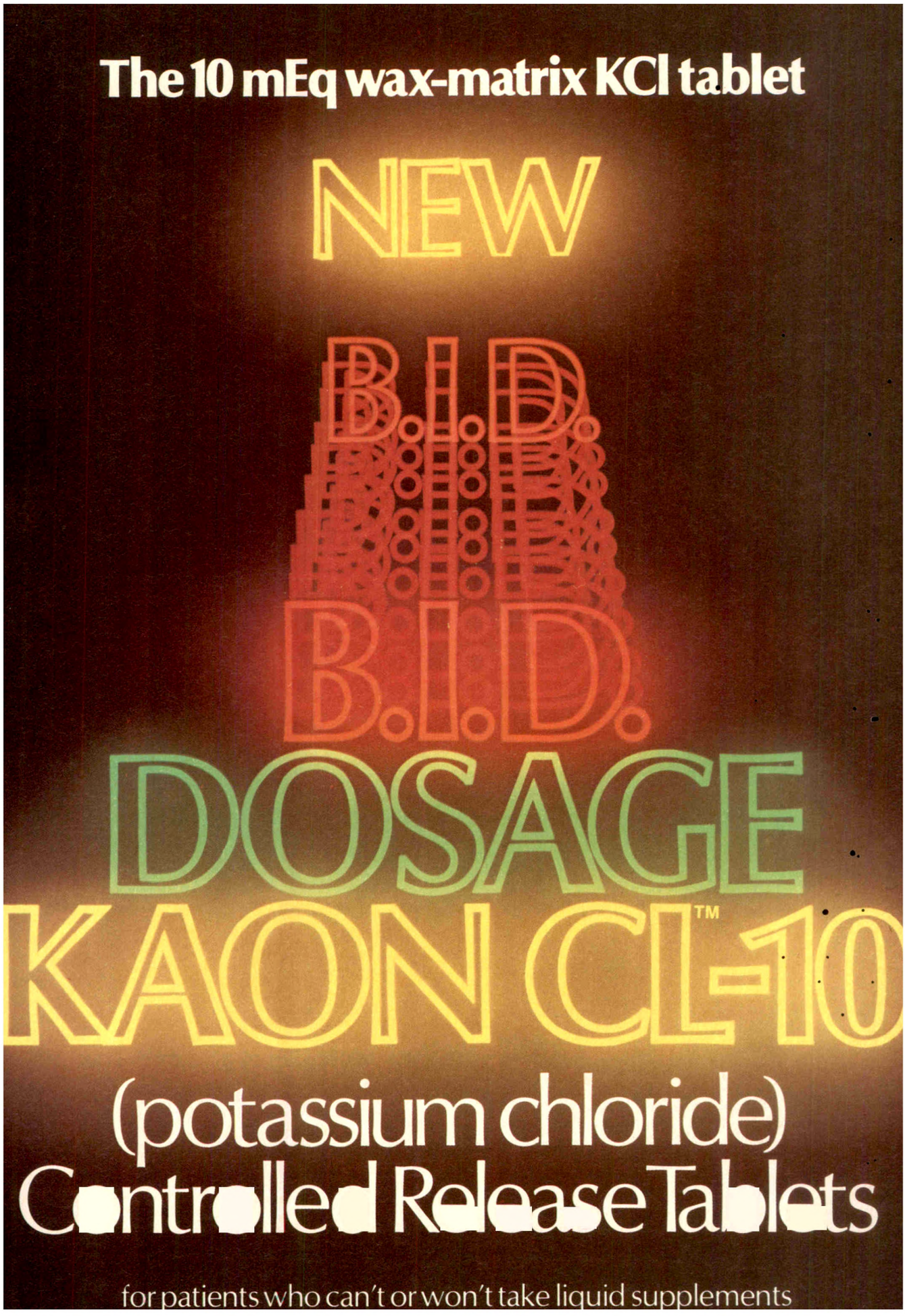
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CLINICAL STUDIES

Left Ventricular Function in Chronic Aortic Regurgitation With Reference to End-Systolic Pressure, Volume and Stress Relations

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Left ventricular muscle and pump performance were evaluated in 12 normal subjects and 21 patients with aortic regurgitation (10 with minimal symptoms and 11 with congestive heart failure). A computer-based quantitative analysis of biplane left ventriculograms was used. Both patient groups had significant aortic regurgitation documented by ventriculography. Contractile function measured by peak systolic stress/end-diastolic volume and end-systolic pressure/volume curves was poorer than that in normal subjects in patients with heart failure but not in asymptomatic patients. When normalized for muscle mass, stroke work was not depressed in either asymptomatic patients (mean ± standard error of the mean 0.008 ± 0.001 joules/g) or patients with heart failure (0.009 ± 0.004) by comparison with the value in normal subjects (0.010 ± 0.001).

Angiographically determined cardiac index (CI) increased with increasing volume overload even though forward cardiac index measured by the Fick method remained essentially unchanged: normal subjects (total CI 3.7 ± 0.4 liters/min per m^2, Fick CI 2.4 ± 0.1); asymptomatic patients (total CI 7.6 ± 0.7, Fick CI 2.3 ± 0.2); patients with heart failure (total CI 9.1 ± 0.82, Fick CI 2.1 ± 0.18). Left ventricular peak stress increased significantly in patients with heart failure (511 ± 55 dynes/cm^2 × 10^{-3}) compared with values in normal subjects (360 ± 33) and asymptomatic patients (428 ± 50).

The combination of decreased muscle function and increased demands on pump function causes a significant increase in end-diastolic pressure only in patients with heart failure (23 ± 2 mm Hg), which results in pulmonary congestive symptoms.

Debate continues about left ventricular contractile performance in volume overload caused by aortic regurgitation.[1–10] Depending on the definitions and measures of contractility used, various authors maintain that contractility is increased,[1] normal[2–5] or decreased.[1–3] Commonly used isovolumic phase indexes may be distorted in severe aortic regurgitation because the isovolumic phase of the cardiac cycle is shortened, but the classic Frank-Starling curve, relating performance to end-diastolic length, may be more reliable. Sagawa et al.[11–13] defined a new measure of contractility based on the relation of end-systolic pressure

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to end-systolic volume. This method is only minimally influenced by preload and afterload and is suitable for evaluation of ventricular performance in volume overload states. We studied left ventricular contractile and pump function in chronic aortic regurgitation, using conventional methods such as stroke work index, ejection fraction and the Frank-Starling relation, as well as the new measure of contractility developed by Sagawa et al.[11]

Methods

Patient selection: Thirty-three subjects were studied: 12 normal subjects and 21 patients with aortic regurgitation (10 who were relatively asymptomatic and 11 who had congestive heart failure).

All 12 normal subjects were studied because of a chest pain syndrome. All 12 had angiographically normal coronary arteries, normal regional wall motion and no evidence of valve or shunt lesions. Their left ventricular end-diastolic pressure was 12 mm Hg or less and their ejection fraction was greater than 50 percent. Their mean age was 46 years (range 20 to 69). There were six men and six women.

Ten patients with significant angiographically judged aortic regurgitation who had only minimal symptoms (New York Heart Association[14] functional classes I and II) were selected for the asymptomatic group. None of these patients had coronary disease or mixed valve lesions. Six had chest pain and five had dyspnea on extreme exertion, but none limited activity because of such symptoms. The mean age of this group was 45 years (range 20 to 71). There were five men and five women.

Eleven patients with angiographic evidence of significant aortic regurgitation associated with symptoms of heart failure at rest or on performing minimal activity (functional classes III and IV) were selected for the group with heart failure. None of these patients had angiographic evidence of coronary artery disease or mixed valve lesions. Four patients had chest pain, 10 had paroxysmal nocturnal dyspnea, 4 had peripheral edema, 2 had syncope and all 11 had dyspnea at rest or on minimal exertion. The mean age of this group was 51 years (range 20 to 71). There were 3 women and 8 men.

Cardiac catheterization: All 33 subjects underwent cardiac catheterization in the fasting state with mild sedation and local anesthesia; either the femoral or the brachial arterial technique was used.[15,16] Aortic and left ventricular pressure measurements were made with dual Millar micromanometer catheters in 15 patients and with fluid-filled catheters connected to Statham (P23Db) pressure transducers in the remaining 18.

Left ventricular pressure was recorded just before angiography with the fluid-filled catheters, and simultaneously with the left ventriculogram when the micromanometer catheter was used. The nonsimultaneous pressure recordings were traced on a digital plotting table and synchronized with the ventriculographic data using the R wave of the electrocardiogram as a reference. We tested the time difference between the micromanometer and fluid-coupled pressure waves measured with similar catheters in two dogs. The peak left ventricular pressure of the fluid-coupled waveform lagged behind the peak of the micromanometer waveform by 13.2 ± 3.1 ms (mean ± standard error of the mean), a lag of less than one cine frame. This delay is not large enough to affect the end-systolic pressure measurement. We have used this method in a previous study and found no difference between the data obtained from the two catheters.[17]

Cardiac output was determined by the Fick method or by cardiogreen indicator dilution curves.

Ventriculographic recording: Monoplane (5 patients) and biplane (28 patients) 35 mm cineventriculograms of the left ventricle were exposed at 60 frames/s. Contrast medium was injected at a rate of 11 to 15 ml/s for 3 seconds. The electrocardiogram and pressure tracings were recorded simultaneously on the cine film with the ventriculogram or on a continuous recorder at a rate of 50 mm/s. A timed light pulse was recorded on the biplane films to provide precise synchronization between the two films during analysis. The monoplane studies were performed in the 30° right anterior oblique position. The biplane studies were performed in both the 30° right and 60° left anterior oblique positions.

Ventriculographic data analysis: Pressure, volume and electrocardiographic data were digitized, frame by frame, using a digital plotting table. To minimize the effects of contrast medium, the earliest well opacified beat was analyzed. For each patient, the left ventricular outline was digitized for 60 to 80 frames representing 1.5 cardiac cycles.[18] Premature ventricular complexes and postpremature ventricular complexes were not analyzed. Left ventricular volume was calculated using the formula of Rackley et al.[19] Stroke work and wall stress were calculated using methods we[18] have previously described in detail.

Statistical analysis: One way analysis of variance was used to compare data from the three groups. Linear regression analysis was performed on the contractile function data.

Results

Hemodynamic data (Table I): Hemodynamic data are presented in Table I. Compared with values in the normal group, mean aortic pressure, left ventricular end-systolic pressure and left ventricular end-diastolic presssure were increased significantly only in the group with heart failure. End-diastolic volume index was increased significantly in both the asymptomatic patients and those with heart failure, but end-systolic volume

TABLE I

Hemodynamic Data in Normal Patients and Patients With Aortic Regurgitation (mean values ± standard error of the mean)

		Aortic Regurgitation	
	Normal (n = 12)	Asymptomatic (n = 10)	Heart Failure (n = 11)
Mean AoP (mm Hg)	87 ± 3	95 ± 4	99 ± 4*
LVSP (mm Hg)	121 ± 5	146 ± 8*	163 ± 5*
EDP (mm Hg)	10 ± 1	9 ± 2	23 ± 2*
ESP (mm Hg)	97 ± 6	111 ± 6	125 ± 5*
EDVI (ml/m^2)	93 ± 6	159 ± 19*	247 ± 18*
ESVI (ml/m^2)	37 ± 3	62 ± 14*	132 ± 14*
SVI (ml/m^2)	58 ± 5	97 ± 8*	114 ± 8*
EF (%)	62 ± 3	65 ± 4	48 ± 3*
CI (liters/m^2)			
Dye dilution	3.3 ± 0.3	3.3 ± 0.4	3.0 ± 0.4
Angiographic	3.7 ± 0.4	7.6 ± 0.7*	9.1 ± 0.8*
CI Fick	2.1 ± 0.1	2.3 ± 0.2	2.1 ± 0.18
ESP/ESVI	2.7 ± 0.2	3.1 ± 0.9	1.0 ± 0.2*
ESS/ESVI	4.5 ± 0.4	4.2 ± 0.8	2.1 ± 0.3*

* $p < 0.05$ compared with value in normal group.

AoP = aortic pressure; CI = cardiac index; EDP = left ventricular end-diastolic pressure; EDVI = end-diastolic volume index; EF = ejection fraction; ESP = end-systolic pressure; ESS = end-systolic stress; ESVI = end-systolic volume index; LVSP = left ventricular systolic pressure; SVI = stroke volume index.

TABLE II

Data on Hypertrophy and Work (mean values ± standard error of the mean)

		Aortic Regurgitation	
	Normal	Asymptomatic	Heart Failure
LVMI (g/m^2)	83 ± 6	180 ± 14*	212 ± 24*
LVM/EDV (g/ml)	0.92 ± 0.10	1.28 ± 0.20	0.83 ± 0.10
h/R	0.31 ± 0.02	0.43 ± 0.05*	0.33 ± 0.02
SWI (joule/m^2)	0.76 ± 0.07	1.44 ± 0.2*	1.76 ± 0.19*
SW/g heart muscle	0.010 ± 0.001	0.008 ± 0.001	0.009 ± 0.004

* $p < 0.05$ compared with normal value.

EDVI = end-diastolic volume index; h = wall thickness; LVMI = left ventricular mass index; R = radius of minor axis; SW = stroke work; SWI = stroke work index.

TABLE III

Myocardial Wall Stress Characteristics (mean values ± standard error of the mean)

		Aortic Regurgitation	
	Normal	Asymptomatic	Heart Failure
PS (dynes/cm^2 × 10^{-3})	360 ± 33	428 ± 50	511 ± 55*
ESS (dynes/cm^2 × 10^{-3})	169 ± 23	191 ± 21	247 ± 20*
EDS (dynes/cm^2 × 10^{-3})	39 ± 3	33 ± 6	76 ± 10*

* $p < 0.05$ compared with normal value.

EDS = end-diastolic stress; ESS = end-systolic stress; PS = peak stress.

index was increased significantly only in the group with heart failure. Stroke volume index was increased significantly from the value in the normal group in both groups of patients with aortic regurgitation. However, ejection fraction was significantly decreased only in the group with heart failure.

The total cardiac index measured angiographically increased with progressive volume overload, but forward cardiac index measured with either Fick or dye-dilution methods did not increase, indicating that a significant proportion of cardiac work was expended on regurgitant volume.

Data on ventricular hypertrophy and work (Table II). Chronic volume overload produced significant myocardial hypertrophy, evidenced by an increase in left ventricular mass index, in both the asymptomatic patients and the group with heart failure. Although the ratio of left ventricular mass to end-diastolic volume was not statistically different among the groups, this ratio was somewhat higher in the asymptomatic group. Wall thickness (h) and minor axis radius (R) were measured at one-half the distance between the aortic valve and apex. The ratio (h/R) was significantly higher than normal in the asymptomatic group. The data on these two indexes suggest that hypertrophy per unit of volume overload was greater in the asymptomatic group than in the group with heart failure.

Stroke work index increased with increased volume overload, whereas stroke work per gram of heart muscle did not. This finding indicates that muscle hypertrophy compensated for excess stroke work and maintained work constant per muscle unit.

Wall stress (Table III): Compared with the value in the normal group, peak wall stress increased by 19 percent in the asymptomatic group and by 42 percent in the group with heart failure, and end-systolic stress increased by 13 and 46 percent, respectively, in two patient groups.

Similarly, compared with the value in the normal group, end-diastolic stress almost doubled in the group with heart failure, but did not increase in the asymptomatic group. From these data, it appears that peak end-systolic and end-diastolic stresses were somewhat normalized by hypertrophy only in the asymptomatic group.

Contractile performance: Left ventricular contractile performance was measured by the Frank-Starling relation and with two Sagawa elastance curves. The Frank-Starling relation of peak systolic stress versus end-diastolic volume index is shown in Figure 1. Estimates of average ventricular function for each group were obtained from the naturally occurring variation in ventricular volume. The effects of wall thickness and

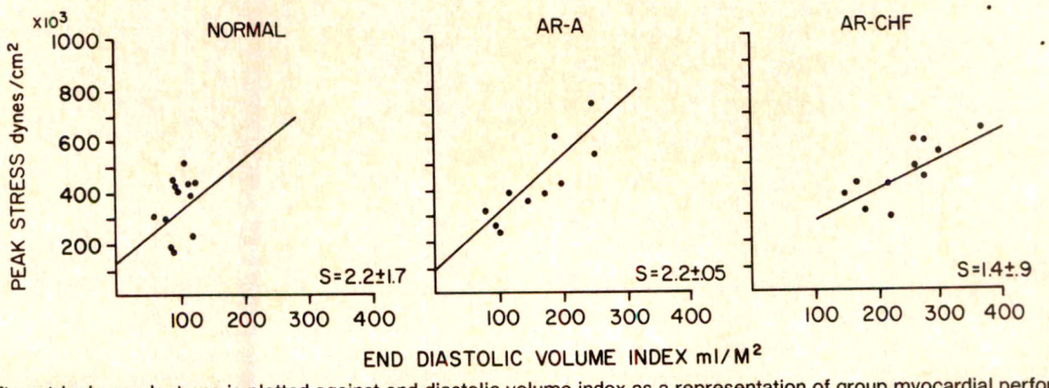

FIGURE 1. Left ventricular peak stress is plotted against end-diastolic volume index as a representation of group myocardial performance. Each point is obtained from one patient in the respective group. The **solid lines** are linear regression estimates of the individual data points. The slope (s) and the standard errors are listed for each group. The slope for the group with heart failure is lower than normal, but the difference is not significant. AR-A = aortic regurgitation, asymptomatic group; AR-CHF = aortic regurgitation, group with congestive heart failure.

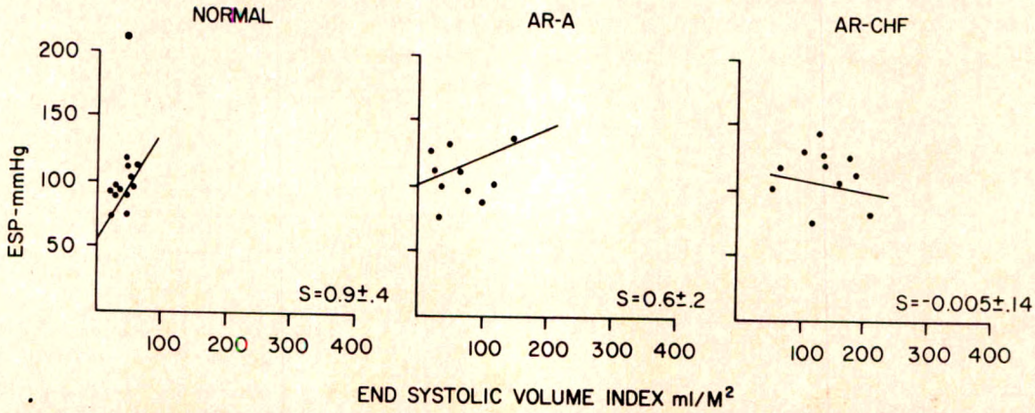

FIGURE 2. Group contractile function expressed by the relation of left ventricular end-systolic pressure (ESP) to end-systolic volume index. Each point is obtained from an individual patient. The **solid lines** are linear regression estimates of individual data points. The slopes and the standard errors are listed for each group. The slope of the group with heart failure is significantly ($p < 0.05$) lower than normal. Abbreviations as in Figure 1.

left ventricular pressure were accounted for by measuring systolic wall stress. The slope of the linear regression for this index was depressed for the group with heart failure in comparison with the other two groups.

The first Sagawa curve[11–13] utilizes the relation between end-systolic pressure and end-systolic volume to describe ventricular performance. The slope of this relation (Emax) is an index of contractility that is minimally influenced by changes in afterload or preload. The naturally occurring variations in end-systolic volume among patients in each group can be used to construct linear regression estimates of the average Emax line (Fig. 2). The slope of this curve was depressed in the group with heart failure, indicating that contractility was decreased in this group. The second Sagawa curve accounts for variations in wall thickness, left ventricular pressure and volume by plotting end-systolic stress against end-systolic volume index (Fig. 3). The slope for the group with heart failure was significantly depressed and the slope for the asymptomatic group was also below normal but not to a statistically significant extent.

With use of the same data, end-systolic pressure/volume and end-systolic stress/volume ratios were calculated for each patient (Table I). Both ratios were significantly decreased in the group with heart failure but not in the asymptomatic group.

Discussion

Our analysis of left ventricular performance in aortic regurgitation indicates that contractile and pump functions are reduced when the chronic volume overload progresses to congestive heart failure, but contractile function appears normal and pump function is not significantly reduced in patients whose chronic volume overload has not yet progressed to congestive heart failure.

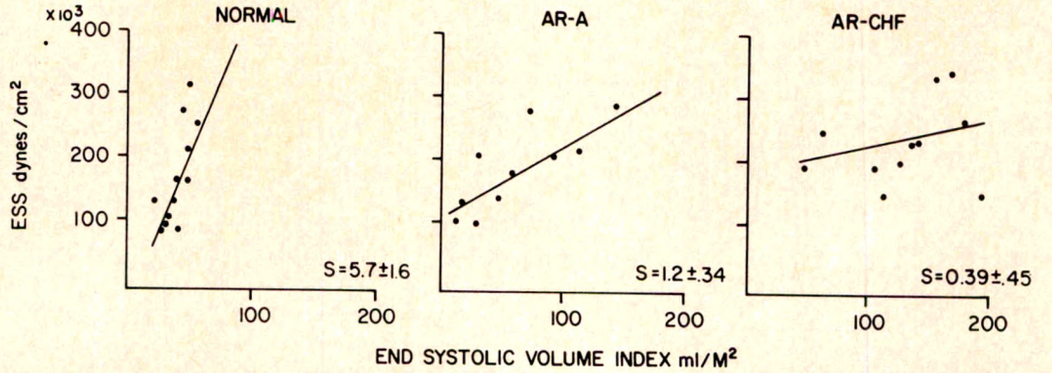

FIGURE 3. Left ventricular end-systolic stress (ESS) plotted against end-systolic volume index as a representation of group myocardial performance. Each point is obtained from one patient in the respective group. The **solid lines** are linear regression estimates of the individual data points. The slopes and the standard errors are listed for each group. The slope of the group with heart failure is significantly ($p < 0.05$) lower than normal. Abbreviations as in Figure 1.

Data on hemodynamics and hypertrophy: Progressive volume overload in our patients with aortic regurgitation produced progressive increases in end-diastolic volume, end-systolic volume and stroke volume. As aortic regurgitation became more severe, stroke volume increased to a level much higher than normal, but end-diastolic volume increased to an even greater degree. Thus, ejection fraction decreased as aortic regurgitation became more severe. These changes suggest that a Frank-Starling type of compensation occurs initially in volume overload, but as the volume overload becomes more severe, the left ventricle is unable to compensate for the overload, pump function begins to fail and congestive heart failure ensues.

Total cardiac index measured angiographically increased with increasing volume overload, but forward cardiac index measured with either the Fick or the dye-dilution method did not increase. Therefore, a significantly greater regurgitant volume accounted for the increase in total cardiac output, but this regurgitant volume was essentially ineffective flow and did not contribute to the metabolic needs of the patient. Nevertheless, considerable myocardial energy is expended to maintain this regurgitant volume, and the heart's ability to function without failing under these conditions indicates that Frank-Starling compensation is effective in asymptomatic patients. However, among patients with heart failure, our data show that decompensation has occurred. This decompensation may be the result of volume overload that is too large for the ventricle to pump effectively, but our data suggest that it is due to reduced contractile performance of the myocardium.

Hypertrophy, measured by mass index and wall thickness, increased with increasing volume overload, and the ratios of mass to end-diastolic volume and wall thickness to minor axis were above normal only in the asymptomatic group. These findings, consistent with those of other investigators,[1,2,6] suggest that there was appropriate hypertrophy in both the symptomatic patients and those with heart failure, although there may be excess hypertrophy in the asymptomatic group. The patients with heart failure had increased wall stress in both systole and diastole, suggesting that further hypertrophy would have been necessary to normalize stress for this group, a finding that is also consistent with the data of other investigators.[3,8,20,21] The asymptomatic group had normal or near normal wall stress in both systole and diastole.

Contractile characteristics: Several measurements have been used to evalute myocardial contractility in volume overload states. Mehmel et al.[1] used the left ventricular pressure derivative, contractile element velocity of shortening and velocity of peak shortening and found that both pressure derivative and shortening velocity were increased in aortic regurgitation while velocity at peak shortening was decreased. Miller et al.[5] used pressure derivative and stroke work/end-diastolic volume ratio and found that patients with a very high end-diastolic volume had a decreased ejection fraction, decreased pressure derivative and decreased stroke work/end-diastolic volume ratio. Other investigators have used exercise, atrial pacing, afterload augmentation with angiotensin, and afterload reduction with nitroprusside to study contractile function in aortic regurgitation.

In patients without heart failure Levinson et al.[6] showed that exercise increased forward flow while decreasing systolic ejection period, peripheral vascular resistance, regurgitant flow and tension-time index, without changing total work. Judge et al.[21] used atrial pacing to vary the heart rate in patients with aortic regurgitation and demonstrated that increased heart rate resulted in decreased end-diastolic pressure, decreased stroke volume, decreased end-diastolic stress, and increased forward cardiac output. In both studies, the extent of these responses was reduced in patients with congestive heart failure. Bolen et al.[2] used afterload augmentation with angiotensin to determine whether a patient's left ventricular function should be classified as compensated or decompensated. Patients who were able to maintain an ejection fraction greater than 50 percent were classified as having compensated myocardial function, whereas those whose ejection fraction fell below 50 percent were classified as having decompensated function. In another study, Bolen and Alderman[10] used afterload reduction with nitroprusside to study left ventricular function and found that the best response to this intervention was from patients with decreased ejection fraction and cardiac output and with increased end-diastolic and mean aortic pressures.

The data from our study suggest that contractile function is decreased in severe aortic regurgitation when evidence of left ventricular failure is found clinically. However, this finding should be interpreted cautiously because changes in afterload and preload may affect the validity of the indices we used to evaluate contractile function. Table I shows that mean aortic and left ventricular systolic pressures were elevated in both groups of patients with aortic regurgitation, indicating that afterload as well as preload was altered in these patients. We used several measures of contractile performance to account for or to avoid these effects. The Frank-Starling relation of peak stress versus end-diastolic volume index accounts for preload by incorporating preload into the index while use of stress as the performance index accounts for the increased wall thickness encountered in aortic regurgitation. The relation between end-systolic pressure and end-systolic volume has also been used as an index of contractile performance.[23,24] This relation, described by Sagawa et al.[11–13] is thought to be independent of preload and afterload. To account for the wall thickness variations in the Sagawa index, we used end-systolic stress as well as end-systolic pressure to determine the contractile state of the ventricle. Although the Frank-Starling relation suggested decreased performance, the two Sagawa type relations clearly indicate that ventricular function is depressed in severe aortic regurgitation when heart failure is evident clinically.

Possible limitations of method: Although the three performance curves we used provide useful information

on ventricular performance, there are some limitations to this technique. To compare the three groups, we assumed that the normal curves are linear over the range of volumes measured in all three groups. This assumption allowed us to compare the two groups of patients with aortic regurgitation with the normal group by assuming they functioned on a different curve of contractility when the slopes were different. In addition, we used the natural variation in end-diastolic and end-systolic volume among the patients to calculate the linear regression estimates of the data. The slopes were compared statistically to eliminate observer bias. In addition to these indexes, the ejection fraction was measured and found to be reduced only in the patients with aortic regurgitation who had heart failure.

Clinical implications: Our data indicate that hypertrophy alone does not result in decreased myocardial performance. There appears to be a degree of volume overload and of hypertrophy related with normal function; however, severe overload with further hypertrophy results in decreased myocardial performance and clinical evidence of congestive heart failure. In both states, the degree of hypertrophy is appropriate for the overload, but in the severe overload state, muscle performance is reduced and the ventricle fails.

Although we were unable to follow up these patients longitudinally, the data suggest that patients with aortic regurgitation progress to a symptomatic state when the regurgitant volume becomes greater and the end-diastolic volume and pressure increase. In association with these changes, the systolic myocardial stress increases, the degree of hypertrophy relative to end-diastolic size returns to normal and the ejection fraction decreases. Some of these changes can be detected by noninvasive measurement of left ventricular dimensions. Longitudinal evaluation of left ventricular dimensions and performance using noninvasive techniques may provide useful information regarding the need for surgical correction of the valve lesion in chronic aortic regurgitation.

Acknowledgment

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Coronary Sinus Blood Flow at Rest and During Isometric Exercise In Patients With Aortic Valve Disease

Mechanism of Angina Pectoris in Presence of Normal Coronary Arteries

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In 46 patients with aortic valve disease, coronary sinus blood flow wa measured using a continuous thermodilution method both at rest an during isometric handgrip excercise. All patients had normal coronar angiograms. The patients were separated into three groups: Group I, 1 patients with aortic stenosis (systolic gradient 72 ± 12 mm Hg); Grou II, 15 patients with both aortic stenosis and regurgitation; Group III, 1 patients with aortic regurgitation. At rest, the coronary sinus blood flo was two to three times normal. However, when corrected for left ven tricular mass (ml/100 g), flow was within normal limits. The ratio diastoli pressure-time index/systolic pressure-time index (DPTI/SPTI) was de creased in all three groups at rest. During isometric exercise, coronar sinus blood flow increased significantly: by 60 percent in Group I, by 8 percent in Group II and by 118 percent in Group III. There was a significar reduction of the DPTI/SPTI ratio.

Of the 18 patients with angina on effort during the test, 7 were in Grou I, 6 in Group II and 5 in Group III. There were no differences in the coronar sinus blood flow between the patients with angina and those who wer pain-free, either at rest or during exercise. Angina pectoris does not appea to be caused by a failure of coronary blood flow to increase. There wa no discrepancy between myocardial demand, as measured by the pres sure-time index and coronary blood flow. However, the DPTI/SPTI rati was significantly lower during exercise in the patients with angina tha in those who were pain-free. Underperfusion of the subendocardial muscl seems to be a causative factor in the patients with angina.

Angina pectoris is a common symptom in patients with aortic valv disease. Coronary angiography has demonstrated a relation betwee angina and coronary artery disease. However, many patients with bo severe aortic valve disease and angina pectoris have normal corona arteries. Several mechanisms have been suggested to account for angi in such patients. The few previous studies of coronary blood flow patients with aortic valve disease have been inconclusive. Experiment work on anesthetized dogs[1,2] demonstrated a decrease in mean corona flow in the presence of marked aortic regurgitation, whereas oth studies[3–5] have demonstrated increased coronary blood flow as compar with normal dogs. Foltz et al.[3] demonstrated a reversal of the normal high ratio of diastolic/systolic coronary flow in the presence of acu aortic regurgitation in dogs. Clinical studies[6–8] demonstrated an i creased coronary flow in patients with aortic regurgitation. In view the diversity of opinion and in order to study the mechanism of angi pectoris, we attempted to reinvestigate this question.

Methods

Study patients: Sixty-one patients were studied; 15 of the 61 were exclud because they had coronary artery disease, and the remaining 46 were classifi into three groups: Group I, 12 patients with aortic stenosis; Group II, 15 patier

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with aortic stenosis and regurgitation; and Group III, 19 patients with aortic regurgitation. Eighteen patients complained of angina during exercise. Of these, 7 were in Group I, 5 in Group II and 6 in Group III. Coronary sinus blood flow and myocardial oxygen uptake at rest in the 46 patients were compared with values obtained from a previous study[14] of 13 normal persons.

Hemodynamic measurements: Cardiac catheterization was performed at rest after intravenous premedication with 100 mg of chlorozepate. Pressures were measured using Statham P23dB transducers and were recorded using an Electronics for Medicine VR 12 recorder. Right-sided pressures were obtained using Cournand catheters and left-sided pressures using Brockenbrough catheters. In patients with aortic stenosis, a transseptal approach was adopted, the catheter crossing the atrial septum and mitral valve. In patients with aortic regurgitation, the left ventricle was approached in retrograde manner. In all patients the aortic pressure was measured using a pigtail catheter, positioned just above the aortic valve. Aortic and left ventricular pressures were measured simultaneously. Cardiac output was assessed by the Fick method. A special 7F thermistor catheter was introduced into the coronary sinus in order to determine the coronary sinus blood flow, as described by Ganz et al.,[9] using a continuous thermodilution method.

Measurements of coronary sinus blood flow: Two measurements of coronary sinus blood flow were made at rest in each patient. Blood samples were taken from the coronary sinus and the aorta to determine their oxygen contents, CvO_2 and CaO_2, respectively. Isometric exercise was performed, handgrip being maintained at 50 percent of the maximal effort. The patient was in each case asked to speak loudly throughout, in order to exclude any Valsalva effect. Between the 3rd and 5th minutes, blood samples were again withdrawn and simultaneous aortic and left ventricular pressure measurements repeated. The position of the catheter in the coronary sinus was ascertained by injection of contrast medium.

Angiographic measurements: Single plane left ventricular cineangiography was performed at rest in the 30° right anterior oblique position. End-diastolic and end-systolic left ventricular volumes were measured and the ejection fraction was calculated using Simpson's rule and with the aid of the Philips Grafomed computer system. Left ventricular mass was obtained as described by Kennedy et al.[10].

The aortic regurgitant fraction (RF) was obtained using the formula:

$$RF = SV_A - SV_F / SV_A \times 100.$$

where SV_A is the total stroke volume as determined with angiography and SV_F is the stroke volume obtained by dividing the cardiac output by heart rate. It is assumed that the heart rate at the time of cardiac output measurement was the same as that during left ventriculography.

Aortic valve area was calculated from Gorlin's formula. It was noted that the valve area would be underestimated when aortic incompetence was present. Peak systolic wall stress (T) was determined from Laplace's equation: T = P.r/2d where P = intraventricular wall thickness. The internal left ventricular radius was derived from volume measurement as follows: $r = \sqrt[3]{3.V/4\pi}$.

The diastolic pressure-time index (DPTI) and the systolic pressure-time index (SPTI) were derived from simultaneous aortic and left ventricular pressure recordings. The DPTI/SPTI ratio was calculated as described by Buckberg et al.[11–13] and represents the ratio myocardial oxygen supply/myocardial oxygen demand. Myocardial oxygen uptake ($M\dot{V}O_2$) was calculated using the equation: $M\dot{V}O_2 = CSBF \times (CaO_2 - CvO_2)$.

Selective coronary angiography was performed using the Judkins technique.

Analysis of paired data and statistical significance was performed using Student's paired *t* test and the HP 9815 computer program.

Results

Findings at Rest

Hemodynamic and volumetric data (Table I, Fig. 1): At rest, the heart rate, cardiac index and left ven-

TABLE I

Hemodynamic Data in 46 Patients With Aortic Valve Disease (mean values ± standard error of the mean)

State	HR	CI	LVP	LVEDP	SPG	RF	LVEDV	EF	d	LVM
				Group I (12 patients)						
C	74 ± 3.2	3.05 ± 0.4	191 ± 14	18 ± 2.6	72 ± 12	–	103 ± 10	67 ± 5	13.5 ± 1.1	181 ± 17
E	99 ± 5†		217 ± 15†	27 ± 5*	72 ± 11					
				Group II (15 patients)						
C	70 ± 2.5	2.4 ± 0.15	190 ± 11	21 ± 3	65 ± 10	53 ± 7	149 ± 15	62 ± 3	13.3 ± 0.7	213 ± 22
E	94 ± 3.2†		216 ± 12†	32 ± 5†	66 ± 12					
				Group III (19 patients)						
C	74 ± 3	2.8 ± 0.2	141 ± 5	17 ± 2	–	59 ± 6	205 ± 17	57 ± 3	10 ± 0.6	189 ± 18
E	104 ± 4†		184 ± 10†	29 ±4†						
				p Values						
I vs II	NS	NS	NS	NS	NS	–	<0.05	NS	NS	NS
II vs III	NS	NS	<0.01	NS		NS	<0.05	NS	<0.01	NS
I vs III	NS	NS	<0.01	NS			<0.01	NS	<0.05	NS

* Probability (p) <0.05.† p <0.01.
C = control; CI = cardiac index (liters/min per m^2); d = myocardial thickness (mm); E = exercise; EF = ejection fraction (%); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEDV = left ventricular end-diastolic volume index (ml/m^2); LVM = left ventricular mass (g/m^2); LVP = left ventricular peak systolic pressure (mm Hg); NS = not significant; RF = regurgitant fraction (%); SPG = systolic pressure gradient across the aortic valve (mm HG).

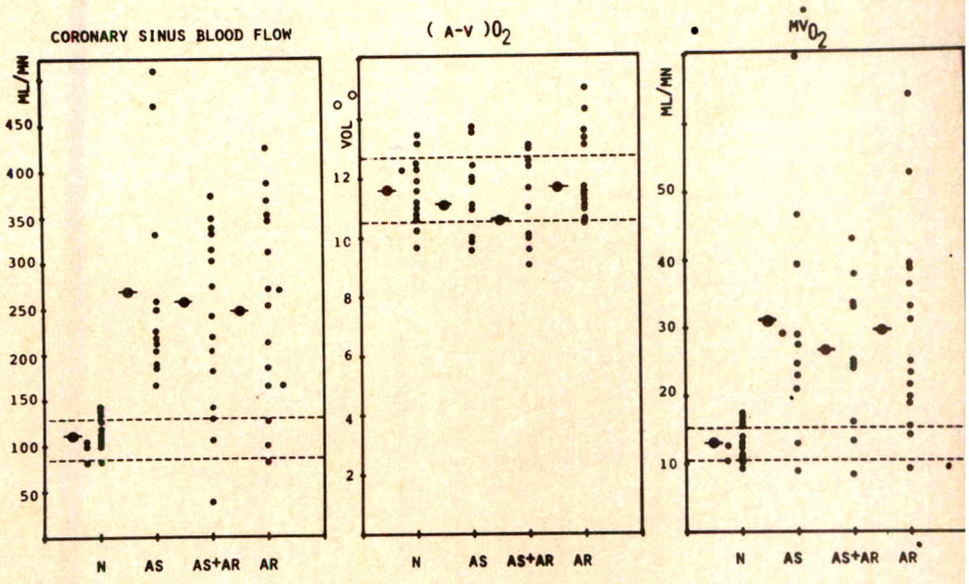

FIGURE 1. Coronary sinus blood flow, arteriovenous oxygen difference [$(A\text{-}V)O_2$] and myocardial oxygen uptake ($M\dot{V}O_2$) at rest in 13 normal subjects and 46 patients with aortic valve disease. **Broken lines** indicate normal range. AR = aortic regurgitation; AS = aortic stenosis; N = normal.

tricular end-diastolic pressure were similar in all three groups of patients. Left ventricular end-diastolic pressure was increased in these groups, but no patient manifested heart failure. The ejection fraction and cardiac index were within normal limits except in patients in Group II (aortic stenosis and regurgitation), whose cardiac index fell slightly. The systolic ejection gradient across the aortic valve was similar in Group I (aortic stenosis) and Group II (aortic regurgitation). The regurgitant fraction was not significantly different in Group II and Group III. There was a marked increase in left ventricular end-diastolic volume among patients in Group III, values being greater than in Group I.

Left ventricular mass and wall stress: The left ventricular mass was greater than normal, but there were no significant differences among the three groups. The mass/volume ratio was greater than normal in patients in Groups I and II, but was less than normal in patients in Group III. Myocardial thickness was less in Group III than in Groups I and II. There were no significant differences in peak systolic wall stress among the three groups.

Coronary sinus blood flow: Coronary flow was higher in patients with aortic valve disease than in normal subjects (Table II). Figure 1 shows that coronary sinus blood flow generally reached two to three time

TABLE II

Coronary Sinus Blood Flow, Myocardial Oxygen Uptake and DPTI/SPTI Ratio in Normal Subjects and Patients With Aortic Valve Disease (mean values ± standard error of the mean)

State	CSBF (ml/min)	CSBF (ml/min per 100g)	CaO_2-CvO_2 (vol%)	$M\dot{V}O_2$ (ml/min)	DPTI/SPTI
			Normal Group (13 patients)		
Rest	111 ± 5.3	128 ± 5	11.6 ± 0.32	13 ± 0.57	—
			Group I (12 patients)		
C	268 ± 32	163 ± 25	11.1 ± 0.6	31 ± 4.6	0.63 ± 0.06
E	419 ± 52		11.3 ± 0.5	47 ± 5.7	0.47 ± 0.05
			Group II (15 patients)		
C	257 ± 25	144 ± 24	10.6 ± 0.5	26.6 ± 2.7	0.66 ± 0.05
E	405 ± 39		10.7 ± 0.05	47 ± 18	0.45 ± 0.04
			Group III (19 patients)		
C	246 ± 23	151 ± 19	11.7 ± 0.5	29 ± 3.4	0.75 ± 0.07
E	462 ± 44		11.6 ± 0.46	57 ± 6.2	0.48 ± 0.07
			p Values		
I vs II	NS	<0.05	NS	NS	NS
II vs III	NS	NS	NS	NS	NS
I vs III	NS	NS	NS	NS	NS
C vs E			$p < 0.01$		

C = control; $CAO_2 - CvO_2$ = arterial-coronary venous oxygen difference; CSBF = coronary sinus blood flow; DPTI/SPTI = diastolic pressure-tim index/systolic pressure-time index ratio; E = exercise; $M\dot{V}O_2$ = myocardial oxygen uptake (ml/min); NS = not significant; p = probability.

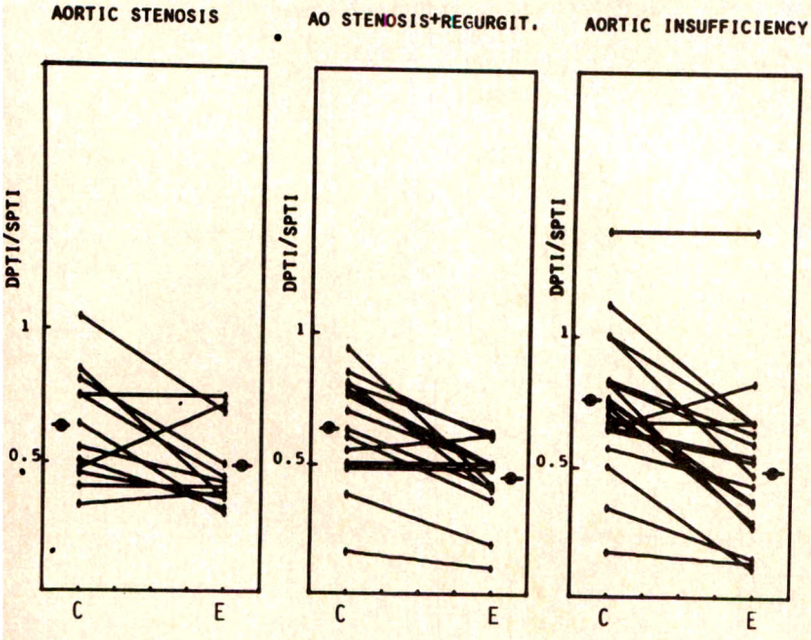

FIGURE 2. Diastolic pressure-time index/systolic pressure-time index (DPTI/SPTI) ratio at rest and during exercise in patients with aortic valve disease. AO = aortic; C = control; E = exercise; regurgit. = regurgitation.

ormal values. There were no significant differences mong the three groups of patients with aortic valve isease. The coronary arteriovenous oxygen difference as the same in patients with aortic valve disease as in ormal subjects. In view of the increased coronary blood ow in the patients with valve disease, this finding reects a significantly increased myocardial oxygen upake.

The apparent increase in the coronary flow can be rrected for left ventricular mass as flow per 100 g of ft ventricular myocardium. The flow per unit mass on is basis is not significantly higher than in normal ubjects. There was no correlation between coronary nus blood flow and ventricular function (as measured y cardiac index and ejection fraction) or between corary flow and peak systolic wall stress or the mass/olume ratio. The DPTI/SPTI ratio was decreased in e three groups and was lower than the critical value .7) initially assigned by Buckberg et al.[13] to patients assified in Groups I and II.

ndings During Isometric Exercise

The hemodynamic and coronary sinus blood flow anges during handgrip exercise are summarized in ables I and II. There were significant increases in heart te, peak left ventricular systolic pressure and left ntricular end-diastolic pressure ($p < 0.01$). There was change in the systolic pressure gradient across the rtic valve in patients in Groups I and II.

Coronary sinus blood flow was significantly increased <0.01) in the three groups: by 60 percent in Group by 88 percent in Group II and by 118 percent in Group .

The coronary arteriovenous oxygen difference was changed, but the myocardial oxygen uptake was inased in proportion to the increased coronary sinus blood flow. The DPTI/SPTI ratio decreased significantly ($p < 0.01$) to very low values (mean less than 0.5) (Fig. 2).

Comparison of patients with and without angina (Table III): Eighteen patients (seven in Group I, five in Group II and six in Group III) had angina on effort. In none of the three groups were there differences between patients with and without angina in left ventricular end-diastolic volume, left ventricular mass or ejection fraction. In Groups I and III, left ventricular peak systolic pressure was higher in patients with than in those without angina. In Group III, left ventricular end-diastolic pressure was greater in the patients with than in those without angina. Patients whose aortic stenosis was complicated by angina had a greater systolic pressure gradient across the valve than did other patients in the same group.

With the exception of patients with aortic regurgitation, no differences in values at rest for coronary sinus blood flow or the DPTI/SPTI ratio were found between the patients with and without angina. In the presence of aortic regurgitation, patients with angina had a lower DPTI/SPTI ratio. During isometric excercise, coronary flow was the same in the two groups, but the DPTI/SPTI ratio was lower in patients with than in those without angina (Fig. 3). Hence it appears that the DPTI/SPTI ratio was more reliable than coronary flow as an indicator of the presence of angina.

Discussion

Coronary blood flow at rest in aortic valve disease: Our results indicate that coronary sinus blood flow and myocardial oxygen uptake, in a group of patients with aortic valve disease, are significantly higher than in a control group of normal subjects. The apparent increase is a consequence of the greater left ventricular

TABLE III

Comparison of 18 Patients With and 28 Patients Without Angina Pectoris (mean values ± standard error of the mean)

	CI	LVP	LVEDP	LVEDV	EF	SPG	PSWS	LVM
				Group I (12 patients)				
Angina (n =)	2.3 ± 0.4	215 ± 48	22 ± 7.7	88 ± 18	70 ± 6	91 ± 17	203 ± 8	180 ± 24
No angina (n =)	3.1 ± 1.4*	158 ± 20*	13 ± 9	124 ± 42	64 ± 11	45 ± 7*	204 ± 7	181 ± 28
				Group II (15 patients)				
Angina (n = 5)	2.2 ± 0.6	205 ± 41	22 ± 12	117 ± 29	61 ± 4	72 ± 7	248 ± 6	167 ± 26
No angina (n = 10)	2.5 ± 0.6	182 ± 46	21 ± 12	170 ± 64	61 ± 5	60 ± 13	235 ± 5	216 ± 21
				Group III (19 patients)				
Angina (n = 6)	3.15 ± 0.8	158 ± 26	26 ± 11	187 ± 48	58 ± 7	—	265 ± 6	179 ± 35
No angina (n = 13)	2.7 ± 0.9	136 ± 17*	14 ± 6†	212 ± 85	57 ± 3		245 ± 5	195 ± 23

* Probability (p) <0.05; p <0.01.
CI = cardiac index (liters/min per m^2); EF = ejection fraction (%); LVEDP = left ventricular end-diastolic pressure (mmHg); LVEDV = left ventricular end-diastolic volume index (ml/m^2); LVM = left ventricular mass (g/m^2); LVP = left ventricular peak systolic pressure (mm Hg); PSWS = peak systolic wall stress (g/cm^2); SPG = systolic pressure gradient across the aortic valve (mm Hg).

mass, the coronary sinus blood flow per 100 g of left ventricular myocardium being within normal limits.

These results are consistent with those of previous investigations in which myocardial blood flow per unit mass was measured at rest. Rose et al.[8], using nitrous oxide, studied seven patients with aortic stenosis and four with aortic regurgitation. They found the flow per unit mass to be the same for these patients as for normal subjects. Other authors, using nitrous oxide,[15,16] iodoantipyrine-131,[17,18] argon,[19] and hydrogen,[20] reported significantly different values for patients with aortic stenosis and normal control subjects. However, Johnson et al.[21] found the myocardial blood flow per unit mass to be reduced in 10 patients with aortic stenosis. The difference between these results may be accounted for by differences in methods. Johnson et al. measured myocardial perfusion using radioactive xenon-131 and a multiple crystal scintillation camera. We used the continuous thermodilution method, which measures flow from all parts of the myocardium draining to the coronary sinus. Thus the thermodilution method measures flow in the left ventricle, which is particularly involved in aortic valve disease.

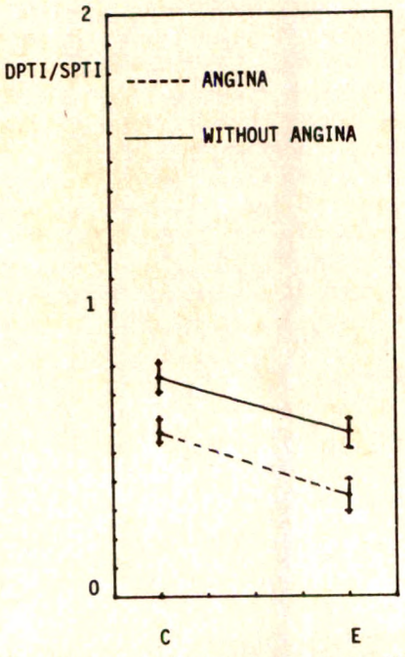

FIGURE 3. Comparison of DPTI/SPTI ratio in patients with and without angina pectoris; C = control; E = exercise.

Methodologic problems: At rest, the catheter was carefully positioned, there were no problems. During isometric excercise, shifts in catheter position can alter apparent flow by the inclusion or exclusion of some of the venous drainage vessels. In our study, the position of the catheter in the coronary sinus was carefully checked during the exercise test.

In 1978, Mathey et al.[22] demonstrated significant reflux of right atrial blood into the coronary sinus during ventricular pacing or rapid atrial pacing and during pulmonary arterial constriction. In view of this finding one might wonder whether the handgrip exercise test induces reflux into the coronary sinus. In order to exclude any Valsalva effect, each patient was asked to count in a loud voice. After the study was completed, a 7F Cournand catheter was introduced into the right atrium which was thereby injected with 10 ml of cold saline solution both at rest and during a second exercise test. In no case was there a change in coronary sinus blood temperature; hence, coronary sinus reflux was excluded as a source of error from our study.

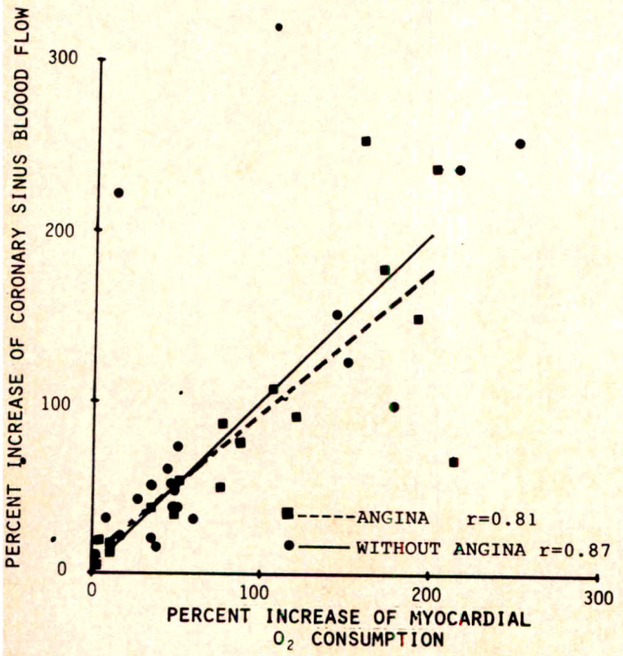

FIGURE 4. Relation between the myocardial oxygen supply (coronary sinus blood flow) and demand (myocardial O_2 consumption) in patients with and without angina.

Coronary blood flow during handgrip exercise n aortic valve disease: Handgrip exercise is not gen-rally thought to be a satisfactory stress test. In our tudy, handgrip exercise induced a slight but significant p <0.01) increase in heart rate, which reached 100 beats/min, as well as significant increases in left ven-ricular pressures. The pressure-rate product (left entricular peak systolic pressure × heart rate) rose ignificantly; by 53 percent in patients with aortic ste-osis and by 83 percent in patients with aortic regurgi-ation. There were significant increases in coronary inus blood flow; 60 percent in Group I, 88 percent in roup II and 118 percent in Group III.

To our knowledge, there have been few previous tudies of coronary blood flow during exercise in pa-ients with aortic valve disease. Rowe et al.[8] measured oronary blood flow during exercise performed on a icycle ergometer, but they induced a lesser tachycardia. hey found increases of 49 percent in patients with ortic stenosis and of 42 percent in those with aortic egurgitation. Although it has been reported that andgrip exercise is less valuable than dynamic exercise, andgrip testing is both simple and clinically conve-ient. Kivowitz et al.[23] measured a 46 percent increase n coronary sinus blood flow during a 5 minute handgrip xercise test during which 25 percent of the maximal oluntary contraction was maintained by seven patients ith coronary artery disease. At 30 percent of the aximal voluntary contraction, Katori et al.[24] observed n increased coronary sinus blood flow averaging 19.8 ercent in 21 patients with various diseases. In light of ese values, it appears that the usual response to this form of exercise was observed in our patients with aortic valve disease. It also appears that the reserve capacity of vasodilatation is unimpaired in these patients as is the ability of the heart to adjust its coronary flow by autoregulation in response to exercise.

Mechanism of angina pectoris in patients with aortic valve disease: The mechanism remains unclear. Fallen et al.[18] suggested that angina occurs because myocardial oxygen consumption exceeds the available supply. It is well known that three main factors determine myocardial oxygen consumption: heart rate, left ventricular wall tension and contractility. Various indexes of myocardial oxygen consumption have been calculated. The pressure-time index (product of heart rate and peak systolic pressure) is considered to reflect the myocardial oxygen requirement. Swanton et al.[25] observed that in patients with angina and aortic stenosis but normal coronary arteriograms, manifested significantly higher peak left ventricular pressure, peak systolic gradient and left ventricular end-diastolic pressure, and had a larger left ventricular mass than did a control group of normal subjects. In our study, there were no significant differences in the increases in coronary sinus blood flow and the pressure-time index between patients with or without angina, in any of the three groups (pure aortic stenosis, combined aortic stenosis and regurgitation, and pure aortic regurgitation).

We found that the regression lines for plots of coronary sinus blood flow and myocardial oxygen uptake were similar for patients with and without angina. (Fig. 4). This was also true of plots of coronary sinus blood flow and pressure-time index, demonstrating the validity of this indirect index. These results suggest that angina does not result from an imbalance in myocardial oxygen demand and supply.

The Venturi effect at the coronary ostia has been observed in both aortic stenosis and aortic regurgitation. It can impair or even reverse coronary flow during the cardiac cycle, thus changing the perfusion of the subendocardial layers. It has been previously demonstrated that subendocardial flow is determined by the interplay of the following factors: coronary arterial diastolic pressure, left ventricular intramural diastolic pressure and the duration of diastole. These factors are expressed by the diastolic pressure-time index (DPTI). If one assumes that the systolic pressure-time index (SPTI) is a rough estimate of myocardial demand, the DPTI/SPTI ratio provides an estimate of the supply/demand ratio.

There has been recent controversy about the use of SPTI as an estimate of myocardial oxygen demand,[26,27] and DPTI probably overestimates the actual mean pressure gradient across the coronary bed. Early studies demonstrated subendocardial underperfusion and histochemical evidence of subendocardial ischemia when the DPTI/SPTI ratio was less than 0.7. More recently the critical ratio has been found to approximate 0.4.[27]

Obviously, caution must be exercised when applying the results of animal studies to man. However, in our study, patients with angina pectoris and aortic stenosis,

whose DPTI/SPTI ratio was similar to that of the patients who had no angina at rest, had a reduction of this ratio below the critical value (0.38 ± 0.06) during exercise. In the patients with aortic regurgitation the DPTI/SPTI ratio at rest was significantly lower in the patients with than in those without angina. During exercise, the DPTI/SPTI ratio of the patients with angina and aortic regurgitation was below the critical ratio (0.33 ± 0.22), but the values were widely scattered and the differences insignificant.

Clinical implications: Our data indicate that coronary blood flow and myocardial uptake of oxygen remain within normal limits in patients with aortic valve disease. When patients with and without angina pectoris were compared, no differences in coronary blood flow were detected, either at rest or during exercise. Nor was any discrepancy found in either group between the pressure-time index and coronary blood flow. Thus, our data suggest that underperfusion of the subendocardial muscle is probably one of the most important factors causing angina in these patients. Our study emphasizes the need to obtain more reliable indexes to estimate this problem, because in aortic stenosis, reduction of the myocardial oxygen supply/demand ratio seems to be a fundamental mechanism in depressing left ventricular performance. Our study also emphasizes the special care needed to protect the myocardium and the subendocardium during surgical valve replacement.

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Congenitally Bicuspid Aortic Valve Causing Severe, Pure Aortic Regurgitation Without Superimposed Infective Endocarditis

Analysis of 13 Patients Requiring Aortic Valve Replacement

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Although stenosis and infective endocarditis are commonly appreciated complications of the congenitally bicuspid aortic valve, pure *severe* aortic regurgitation complicating this congenital malformation, unassociated with either stenosis or infection, is not well recognized. Among 189 patients who had aortic valve replacement at the National Heart, Lung, and Blood Institute because of isolated pure aortic regurgitation, the congenitally bicuspid aortic valve, never the site of infective endocarditis, was responsible for the aortic regurgitation in 13 (7 percent). This report describes certain clinical and morphologic findings in 13 men, aged 26 to 65 years (mean 43), who required aortic valve replacement because of severe aortic regurgitation secondary to a noninfected, nonstenotic congenitally bicuspid aortic valve. Although not generally recognized, the noninfected congenitally bicuspid aortic valve is an important cause of pure aortic regurgitation severe enough to warrant aortic valve replacement.

The congenitally bicuspid aortic valve frequently becomes stenotic, and because most stenotic valves are also regurgitant, the most frequent circumstance in which aortic regurgitation is found with this congenital anomaly is in association with aortic valve stenosis.[1] In this situation the aortic regurgitation is usually of only mild or moderate degree. Also, the congenitally bicuspid aortic valve is often the site of infective endocarditis.[1] Although it may be superimposed on a stenotic congenitally bicuspid aortic valve, infective endocarditis far more commonly involves the previously normally functioning bicuspid valve or the one previously only slightly regurgitant.[1,2] The usual consequence of the infection in this circumstance is severe pure aortic regurgitation. Mild degrees of pure aortic regurgitation also are commonly observed in patients with a congenitally bicuspid aortic valve and elevated pressure in the ascending aorta from associated aortic isthmic coarctation. However, *severe* aortic regurgitation due to a nonstenotic and noninfected congenitally bicuspid aortic valve is believed to be decidedly infrequent and, indeed, no reports, to our knowledge, have focused specifically on this complication of the bicuspid valve condition. In this report, we describe observations in 13 men who underwent aortic valve replacement because of severe pure aortic regurgitation unassociated with aortic valve stenosis or infective endocarditis.

Clinical Features of Patients

Clinical findings (Table I): At the time of aortic valve replacement, the ages of the 13 men studied ranged from 26 to 65 years (mean 43). Preoperatively, one patient had been in functional class I (New York Heart Association classification[3]), three patients in class II, eight in class III and one in class IV. The one patient who was asymptomatic preop-

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TABLE 1

Clinical and Operative Observations in 13 Men With Aortic Valve Replacement for Pure Severe Aortic Regurgitation and Noninfected Congenitally Bicuspid Aortic Valve

Case	Age (yr) at AVR	Age (yr) M First Heard	Age (yr) Onset of Cardiac Symptoms	Pressures (s/d) (mm Hg)		Site of AV Cusps	AV Raphe	AV Ca^{++}	AV Wt (g)
				LV	SA				
1	26	17	20	125/25	125/54	R-L	+	0	
2	26	13	21	150/24	150/60	A-P	+	0	1.2
3	28	6	27	200/32	235/70	?		0	1.0
4	30	16	29	135/11	160/55	A-P	0	0	0.9
5	30	27	27	118/6	118/52	R-L	+	0	0.7
6	40	11	35	200/32	200/80	A-P	+	+	2.9
7	46	20	44	125/7	130/50	A-P	+	0	?
8	48	13	40	170/12	170/60	?	+	+	2.2
9	49	20	?	118/5	120/58	R-L	0	0	1.5
10	56	27	27	165/17	165/72	A-P	+	0	1.4
11	57	22	44	160/14	170/75	R-L	+	+	1.8
12	63	45	60	155/7	155/55	?	+	+	2.3
13	65	60	65	138/36	160/53	R-L	+	+	1.7

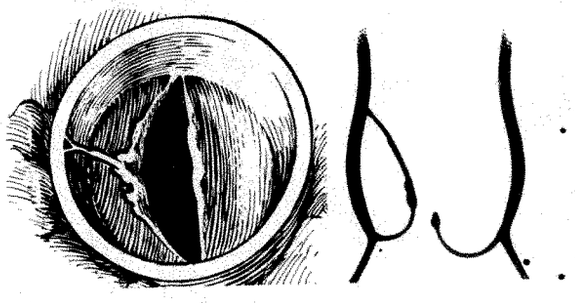
A = anterior; AV = aortic valve; AVR = aortic valve replacement; Ca^{++} = calcium; L = left; LV = left ventricle; M = murmur; P = posterior; R = right; SA = systemic artery; s/d = peak systole/end-diastole; Wt = weight; ? = not known; + = present or positive; 0 = absent or negative.

eratively underwent aortic valve replacement because of severe aortic regurgitation associated with a dilated left ventricular cavity[4] (left ventricular end-systolic cavity dimension on echocardiogram = 56 mm). None of the 13 patients at any time had had clinical evidence of either active infective endocarditis or acute rheumatic fever.

A precordial murmur had been heard for the first time initially as early as age 6 years to as late as age 60 years (mean 23). By auscultation, all 13 patients had grade 3-5/6 murmurs typical of aortic regurgitation, and by aortic root angiograms the degree of aortic regurgitation was graded in each as either 3+/4+ or 4+/4+. The direct aortic diastolic pressures preoperatively ranged from 45 to 80 mm Hg (mean 61). All 13 patients also had basal precordial systolic murmurs, but at catheterization none had a peak systolic pressure gradient between the left ventricle and a major systemic artery or on pullback from the left ventricle to the aorta. Precordial ejection sounds were absent in all 13 patients. Aortic root angiograms were obtained in all patients, but the bicuspid condition of the aortic valve could not be established by this method. Also, the bicuspid nature of the valve was not recognized in any of the seven patients who had echocardiograms.

Three patients (Cases 3, 4 and 6) had aortic isthmic coarctation, with a peak systolic pressure gradient across the coarctation of 70, 50 and 70 mm Hg, respectively. One (Patient 1) had a right aortic arch. No patient had evidence of mitral regurgitation. The father of Patient 2 had had aortic valve replacement because of a stenotic (60 mm Hg peak systolic pressure gradient) congenitally bicuspid aortic valve.

Surgical and morphologic findings: At aortic valve replacement, only two aortic valve cusps were identified in each of the 13 patients (Fig. 1 to 4). In 10 valves, a



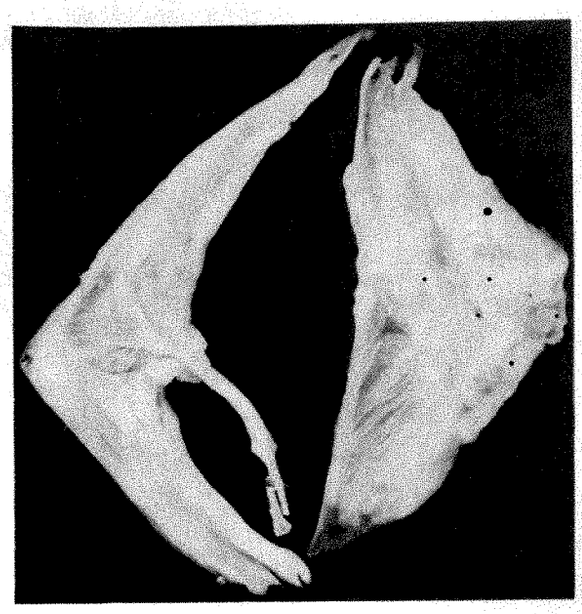


FIGURE 1. Aortic valve in Case 1. The fibrous band on the right cusp (**below**) was attached to the wall of the ascending aorta as shown in the diagram (**above**).

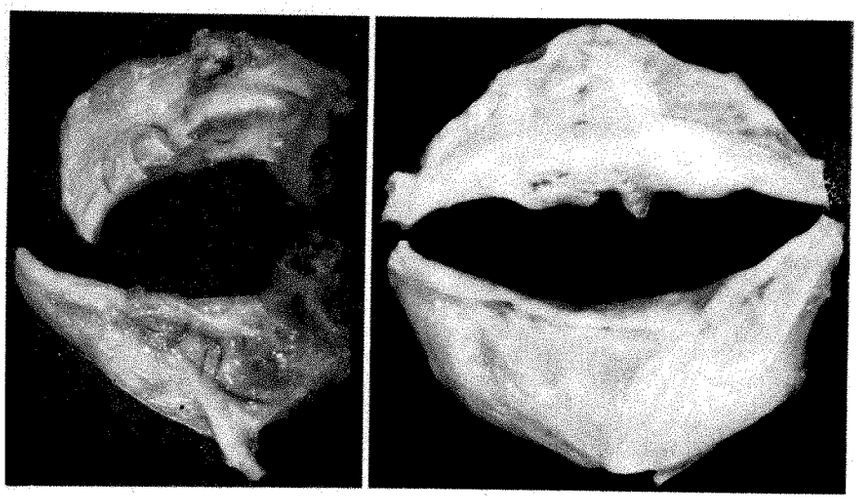
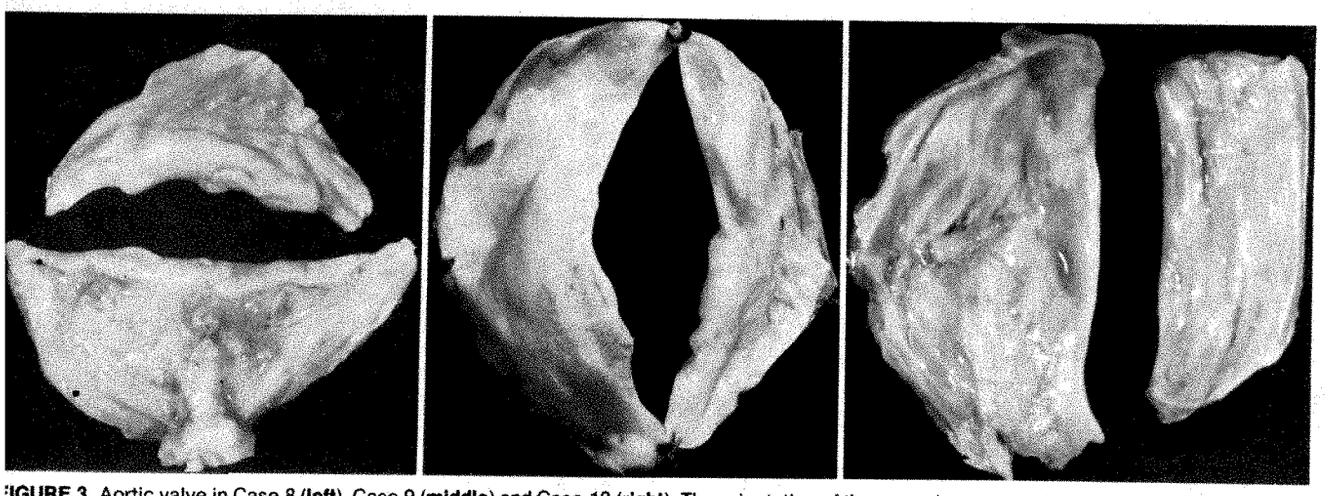


FIGURE 2. Aortic valve in Case 6 (**left**) and Case 7 (**right**). In each valve, the larger cusp is the anterior one. Calcium deposits are present in the valve on the **left**, but not in the one on the **right**.



IGURE 3. Aortic valve in Case 8 (**left**), Case 9 (**middle**) and Case 13 (**right**). The orientation of the cusps is uncertain in Case 8; calcium is present n the raphe in the larger cusp. In both Case 9 and Case 13, the larger cusp is the right one, and the smaller cusp, the left one.

IGURE 4. Aortic valve in Case 12. The orientation of the two cusps this patient is not known. The raphe is calcified.

congenital raphe (false commissure) was identified. Each cusp of all 13 aortic valves was thickened by fibrous tissue; no cusp contained vegetations or perforations, indentations, or other evidences of healed infective endocarditis.[5] Calcific deposits, all small, were present in 5 of the 13 excised aortic valves; the deposits in 3 were limited to the raphes.

Comments

Frequency at necropsy of pure regurgitation in bicuspid aortic valve: Each of the 13 patients had aortic regurgitation severe enough to require aortic valve replacement, and at operation each was found to have a congenitally bicuspid aortic valve that neither was stenotic nor had evidence of past infective endocarditis. Furthermore, no patient had had a past clinical illness compatible with active infective endocarditis. Among the complications of a congenitally bicuspid aortic valve, pure severe aortic regurgitation unrelated to infective endocarditis is the least common. Among 200 patients

over age 15 years with a congenitally bicuspid aortic valve studied by one of us (W.C.R.) at *necropsy*, only 3 had pure severe aortic regurgitation unassociated with infective endocarditis.[1] Of the 200 necropsy patients, however, 179 had some degree of aortic regurgitation, but it was associated with aortic valve stenosis in 157 and was the result of infective endocarditis in 19; in the remaining 21 patients the bicuspid valve functioned normally. Of 152 necropsy patients with a congenitally bicuspid aortic valve reported on by Fenoglio et al.,[6] 4 apparently had pure aortic regurgitation without evidence of infective endocarditis; however, the severity of the aortic regurgitation in their patients was not stated.

Frequency of congenitally bicuspid valve in pure aortic regurgitation (operative experience): Although the two studies cited provide some information on the frequency of pure aortic regurgitation unassociated with infective endocarditis among *necropsy* patients with a congenitally bicuspid aortic valve, no information is available concerning the frequency of the congenitally bicuspid aortic valve unassociated with infective endocarditis among patients with pure *severe* aortic regurgitation. Accordingly, we reviewed the clinical and operative records and the excised aortic valves in 189 patients aged 18 to 70 years who had aortic valve replacement at the National Heart, Lung, and Blood Institute from 1963 to 1979 because of *isolated* (unassociated with dysfunction of another cardiac valve) *pure* (no element of valve stenosis) aortic regurgitation (Table II). In 13 (7 percent) of the 189 patients the aortic regurgitation was the result of a congenitally bicuspid aortic valve that was not and had not been the site of infective endocarditis. In contrast to the 13 patients that form the basis of this report, only 7 patients (among the 189) had pure aortic regurgitation because of infective endocarditis involving a congenitally bicuspid aortic valve. Thus, the congenitally bicuspid aortic valve unaffected by infective endocarditis is an important cause of pure aortic regurgitation severe enough to warrant aortic valve replacement.

TABLE II

Etiology of Isolated Pure Aortic Regurgitation in 189 Patients Aged 18 to 70 Years Having Aortic Valve Replacement

Cause	Patients n	Patients %
1.* Rheumatic	94	49
2.* Infective endocarditis	41	22
Bicuspid (n = 7)		
Tricuspid (n = 34)		
3. Marfan and Marfan-type	15	8
4.* Congenital (bicuspid valve)	13	7
5.* Prolapse from ventricular septal defect	10	5
6. Syphilis	9	5
7. Aortic dissection	2	
8. Ankylosing spondylitis	2	
9.* With subaortic stenosis	2	7 4
Discrete subaortic stenosis (n = 1)		
Hypertrophic cardiomyopathy (n = 1)		
10. Trauma	1	
Total	189	100

* Aortic regurgitation resulted from abnormality of the aortic valv only and not from abnormality of the aorta.

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Delayed Pericardial Disease After Radiotherapy

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Delayed chronic constrictive pericarditis developed in seven patients 51 to 268 (mean 116) months after radiotherapy. Six of the seven complained of exertional dyspnea that was initially believed to be caused by mediastinal fibrosis. All patients had raised jugular venous pressure, although in two patients this finding was not appreciated by the primary physician. There were no consistent noninvasively identifiable features to allow prediction of constrictive pericarditis other than consideration of its existence and careful examination of the cardiovascular system. All patients had constrictive pericarditis proved at cardiac catheterization. Of the five patients who underwent pericardiectomy, two had an excellent functional result, one has residual pericardial constriction and two died of unrelated causes. Recommendations for the treatment of radiation-induced pericardial disease are given.

Supervoltage radiation therapy has been administered for more than 2 decades to patients who have breast cancer or Hodgkin's disease. As these patients have established extended survival patterns and cures from their malignancy, the delayed cardiac consequences of this treatment have become recognized. It is generally accepted that transient pericardial effusions represent the most common form of radiation-induced cardiac disease and may be found in as many as 30 percent of patients.[1] This entity characteristically develops within the first 24 months after radiotherapy and usually resolves spontaneously within 2 years without any chronic sequelae.[1,2] Less frequently, effusive-constrictive or chronic constrictive pericarditis may occur. Among 21 patients receiving mediastinal radiotherapy, effusive constrictive pericarditis was noted in 6 patients and chronic constrictive pericarditis in 3.[3] The interval between radiotherapy and the diagnosis of either effusive-constrictive or chronic constrictive pericarditis in that series ranged from 6 to 72 (mean 26.5) months. No instances of such complications were found in another study[2] encompassing 81 patients. Despite the experience indicating the appearance of radiation-induced pericardial disease relatively soon after radiotherapy,[1,2] there have been instances of its delayed occurrence.[3–5] This report emphasizes the clinical spectrum of pericardial disease after mediastinal irradiation as well as the potential for delayed appearance of the disease. The possible pathogenesis of delayed radiation-induced pericardial disease and our recommendations for its treatment are discussed.

Study Patients

Seven patients at the Baltimore Cancer Research Program—National Cancer Institute who manifested radiation-related pericardial disease 51 to 268 (mean 116) months after radiotherapy form the basis of this study. Five of these seven (Cases 2 to 4, 6 and 7) are from a larger group of 81 patients who had Hodgkin's disease treated (before 1974) by anteriorly weighted thoracic mantle radiotherapy; one patient (Case 1) was identified from approximately 70 patients who had Hodgkin's disease treated (since 1974) and had received modified anteriorly weighted thoracic mantle radiotherapy; one patient (Case 5) had received 28 courses of an unknown amount of thoracic radiation 16 years earlier for breast carcinoma. The predominance of Hodgkin's disease in this series reflects a se-

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TABLE I
Clinical Data in Seven Cases

Case	Age (yr) & Sex	Diagnosis*	Therapy†	Interval‡	Type of Heart Disease	Presenting Symptoms
1	47F	HD,NS,3A	4144/28 + MOPP × 6	51 (pericardial window)	E-CP	Fever, dyspnea
				54	CCP	Dyspnea
2	26M	HD,NS,3A$_{EL}$	4538/28 + CVPP ×6 + CNU, VBL ×1 + CVPP ×6	79 (pericardial window)	E-CP	Dyspnea, hypotension
				82 (pericardiectomy)	CCP	Dyspnea
3	31M	HD,NS,3A	4850/36 + MOPP ×5	108 (pericardial window)	E-CP	Pleural/pericardial effusion
				132 (pericardiectomy)	CCP	Dyspnea
4	32F	HD,NS,3A	4905/27 + MOPP ×6	82	CCP	Dyspnea
5	68F	Metastatic breast cancer	Unknown amount/28 + Adm (585 mg/m^2)	264 (pericardial window)	E-CP	Dyspnea, hypotension
				268 (pericardiectomy)	CCP	Dyspnea
6	34M	HD,NS,4A	3874/23 + MOPP ×6	124 (pericardiectomy)	CCP	—
7	23F	HD,NS,4B	4767/44 + MOPP ×3	53 (pericardiectomy)	CCP	Dyspnea
Average			4513/30.5	108.7§		

* At time definitive diagnosis of pericardial disease was made. † Therapy given as mid cardiac dose (rads)/numbers of days total course of radiotherapy given. ‡ Interval (in months) from completion of radiotherapy to recognition of radiation-induced pericardial disease. § Calculated using shortest interval from radiotherapy to confirmed diagnosis of pericardial disease.

Adm = adriamycin; CCP = chronic constrictive pericarditis; CNU = lomustine; CVPP = cyclophosphamide, vincristine, procarbazine, prednisone; E-CP = effusive-constrictive pericarditis; HD = Hodgkin's disease; 3A$_{EL}$ = stage 3A of Hodgkin's disease with limited extension to the lungs; MOPP = nitrogen mustard, vincristine, procarbazine, prednisone; NS = nodular sclerosis; VBL = vinblastine.

lection bias of our institution. The mid cardiac radiation dose in the six patients treated for Hodgkin's disease was 3,874 to 4,905 (mean 4,513) rads. In the patient treated for breast carcinoma 16 years before entry, the radiation dose was unknown. No cause (infectious, neoplastic, collagen vascular or metabolic) for the pericardial reactions other than irradiation was present in any of these seven patients. Although all patients were also treated with chemotherapy, known cardiotoxic drugs were used only in Patient 5, and no evidence of drug-induced cardiac toxicity was found in this patient at autopsy.

Results

Clinical features: The clinical data on the seven patients are summarized in Table I. Five patients (Cases 2 to 5 and 7) complained of moderately severe effort dyspnea; however, only two of them (Cases 5 and 7) had significant mediastinal fibrosis on their chest X-ray film. One patient (Case 6) manifested unexplained pleural effusions and hepatosplenomegaly 9 months before choronic constrictive pericarditis was diagnosed. He was being evaluated for a possible recurrence of his Hodgkin's disease until it was recognized that these signs were caused by chronic constrictive pericarditis. Another patient (Case 1) had signs of acute pericarditis (fever and a pericardial friction rub) and had evidence of cardiac tamponade. A diagnostic surgically produced pericardial window revealed a 500 cc serous pericardial effusion and moderately thickened pericardium (that is, effusive-constrictive pericarditis). Three months after the pericardial window was performed for cardiac tamponade, a Swan-Ganz catheterization showed evidence of constrictive pericarditis. Pericardial effusions were documented 1, 4, 24, and 72 months, respectively, before the diagnosis of chronic constrictive pericarditis in four patients (Cases 3 and 5 to 7). The data from these five patients (Cases 1, 3 and 5 to 7) suggest that chronic constrictive pericarditis occurring after mediastinal radiotherapy is usually preceded by an effusive pericardial reaction that may be present many months earlier.

Noninvasive diagnostic signs: When constrictive pericarditis was diagnosed, all patients had a raised mean jugular venous pressure (more than 10 cm water) by physical examination with collapsing X/Y descent. Two patients (Cases 2 and 4) had a pericardial knock and two (Cases 2 and 3) had distant heart sounds. Noninvasive studies (electrocardiography and M mode echocardiography) did not consistently predict the presence of chronic pericardial disease in these severe patients. The total summed limb lead QRS amplitude by electrocardiogram taken before irradiation as compared with that at the time chronic constrictive pericarditis was diagnosed showed a reduction of 13 to 5 (mean 40.3) percent in six patients (Cases 1 to 3 and 5 to 7) and an increase of 50 percent in one patient (Case 4). All echocardiographic chamber measurements were

TABLE II
Cardiac Catheterization Data in Seven Cases

Case	Pressures (mm Hg) RA (mean)	RV	PA	PCW (mean)
1*	15		36/15	15
2	22	38/24	38/24	24
3	18	30/18	30/18	18
4†				
October 1977	9	26/12	24/11	11
August 1979	7	25/9	24/10	11
5	8	22/11	22/11	11
6‡				
October 1978	19	40/20	40/20	20
April 1980	15	36/18	36/18	17
7	28	48/28	44/28	24

* Swan-Ganz catheterization for respiratory failure 3 months after a pericardial window for cardiac tamponade. † This patient was followed upcloselyand received no cardiac medications during these 21 months. ‡ Signs of pericardial constriction persisted in this patient after his pericardiectomy in October 1978.
PA = pulmonary arterial; PCW = pulmonary capillary wedge pressure; RA = right atrial; RV = right ventricular.

ormal; four patients (Cases 2 to 4 and 6) had paradoxical interventricular septal motion. No patient displayed the "dip-plateau" pattern in the posterior left ventricular wall motion described by others.[6] At cardiac catheterization (Table II), all patients had hemodynamic data compatible with constrictive pericarditis.

Surgical treatment: Five patients (Cases 2, 3 and 5 to 7) underwent pericardiectomy. The indication for operation was incapacitating exertional dyspnea in four patients (Cases 2, 3, 5 and 7) and persistent pulsatile hepatomegaly in one patient (Case 6). Two patients died after operation, one patient (Case 5) two weeks later from respiratory insufficiency caused by pulmonary fibrosis and lymphangitic spread of her breast carcinoma, and the other (Case 7) 3 months later from progressive Hodgkin's disease of the lungs and chemotherapy-induced granulocytopenia. These two patients showed an initial increase (5 to 10 mm Hg) in systolic blood pressure and decrease (3 to 5 cm H_2O) in mean jugular venous pressure postoperatively. There was little change in the degree of dyspnea in either of them. At autopsy, there was no evidence of myocardial fibrosis in either patient; one patient (Case 5) had some residual visceral pericardial constriction.

Two of the three surviving patients (Cases 2 and 3) are doing well 4 and 12 months, respectively, after operation without clinical evidence of pericardial constriction. Their systolic blood pressure has increased by 5 to 13 mm Hg and their mean jugular venous pressure has decreased by 6 to 10 cm H_2O. A third patient (Case 4) has had no significant changes in blood pressure, heart rate, mean jugular venous pressure or degree of hepatomegaly over an 18 month period after his pericardiectomy. A repeat cardiac catheterization has shown hemodynamic evidence of constrictive pericarditis and is believed to have visceral pericardial constriction. The one patient (Case 4) not having surgery has had no significant changes in symptoms, physical findings or hemodynamic measurements during a 21 month follow-up period. She is not being treated with either digitalis or diuretic agents.

Pathology: Review of the pericardial specimens in all of the operative cases revealed thickening and fibrosis. There was no evidence of significant endomyocardial fibrosis in a biopsy of the interventricular septum (Patient 6) or at autopsy in the two patients (Cases 5 and 7) who died. We believe that these morphologic observations make restrictive endomyocardial disease an unlikely cause for the hemodynamic findings in any of these seven patients.

Discussion

Incidence: Previous studies have reported the incidence of radiation-induced pericardial disease to range from 7.7[3,4] to 30[1,2] percent in patients treated with mediastinal irradiation. Characteristically, this entity occurs within the initial 24 to 36 months after radiotherapy and is either an effusive or effusive-constrictive pericarditis. Three of 21 patients with radiation-induced cardiac disease in one study[3] manifested chronic constrictive pericarditis associated with endomyocardial fibrosis 36 to 72 (mean 51) months after mediastinal irradiation. Earlier reports[1,2] from our center included no instances of chronic constrictive pericarditis although the potential for development of this complication was recognized. Our present study indicates that the cardiac consequences of thoracic irradiation may be delayed in appearance for more than 48 months after treatment. Indeed, even if the patient treated with an unknown amount of radiation is excluded from consideration, our patients still experienced a mean interval of 82.8 months between radiotherapy and the earliest clinical recognition of *any* form of heart disease. These delayed cardiac reactions are generally not appreciated by physicians caring for patients who have received mediastinal radiotherapy. Further, none of the patients in the present study were included in an earlier report from our center. In that study,[1] the incidence rate of radiation-induced pericardial effusions in 81 consecutive patients treated with radiotherapy for Hodgkin's disease between 1968 and 1972 was 30.9 percent (25 of 81). Thus, the incidence rate of any type of radiation-induced pericardial disease in these 81 patients is at least 38 percent (31 of 81). We are in the process of performing detailed cardiac evaluations in this entire cohort of 81 patients. It should be reemphasized that six of the seven patients in our study (all but Case 5), as well as all of those previously reported on,[1] were treated by anteriorly weighted or modified anteriorly weighted thoracic mantle field techniques. A potential limitation of these techniques, which is substantiated by our experience, is the production of higher average mid cardiac levels of radiation. Since 1975 equally opposed mantle fields have been employed at our center with a resultant decrease in the average radiation dose received by the heart. Although we have observed a small number of transient pericardial effusions in this group, as yet no instances of effusive-constrictive or chronic constrictive pericarditis have been seen (study in progress).

Pathogenesis: The pathogenesis of radiation-induced myocardial disease has been shown in experi-

mental studies to be caused by a "microvascular ischemia" [4] in which the myocardial capillary bed is obliterated by endothelial cell swelling. The consequence of these changes is ischemia to the myofiber with resultant myocardial fibrosis. By contrast, the pathogenesis of radiation-induced pericardial disease has not been adequately delineated. In addition to the radiotherapy technique used, reactivation of a latent virus within the pericardium,[1] the obstruction of pericardial lymphatics as a consequence of radiotherapy with a resultant effusive pericarditis that organizes and becomes fibrotic,[1] or potentiation of an as yet undefined type of pericardial reaction by adjunctive use of chemotherapeutic agents[1] are possible mechanisms. Further, it is uncertain why radiation-induced pericardial disease appears relatively soon (within months) after irradiation in some patients and may be delayed for extended periods (several years) in other patients. These observations suggest that several different pathophysiologic mechanisms may be responsible for radiation-induced pericardial disease.

Diagnostic clinical features: The recognition of radiation-induced pericardial disease necessitates an awareness of its possible occurrence at any time by physicians caring for patients treated previously with mediastinal irradiation. Six patients (Cases 1 to 5 and 7) in our study experienced dyspnea, and this symptom was incapacitating in four of them (Cases 2, 3, 5 and 7). In two of the four (Cases 5 and 7) chest x-ray examination revealed severe pulmonary fibrosis that was initially believed to be the cause of their dyspnea. The two other patients (Cases 2 and 3) had dyspnea only on strenuous effort. All patients in this study had raised jugular venous pressure with collapsing diastolic descent. In two patients, the external jugular veins were collapsed at a time when the pressure in the internal jugular venous system was 15 cm H_2O. It was not until this discrepancy was sought by careful examination of the jugular veins that the correct diagnosis was made in these patients. Diminished intensity of the heart sounds, the presence of a pericardial knock and diminished QRS voltage in the limb leads were infrequently noted. Paradoxical interventricular septal motion by echocardiography was also not a sensitive finding, being present in only four (Cases 2, 3, 4 and 6) of seven patients.

Nonetheless, a characteristic clinical picture emerges of effusive-constrictive or chronic constrictive pericarditis occurring after mediastinal irradiation. Patients will have mild to moderate exertional dyspnea with or without pleural effusions, hepatomegaly or peripheral edema. All will have raised jugular venous pressure, and some will have distant quality heart sounds. An electrocardiogram often shows diminished QRS amplitude in the limb leads. The echocardiogram will demonstrate a pericardial effusion and thickened pericardium or paradoxic interventricular septal motion, or both, in the patient who has effusive constrictive pericarditis. Cardiac catheterization in these instances will demonstrate diastolic equalization of right heart pressures. Pericardial effusion is usually not found on echocardiography in patients who have constrictive pericarditis although a thickened pericardium or paradoxic interventricular septal motion, or both, may be noted. Except by the absence of known tumor recurrence elsewhere or a long elapsed period of time after initial therapy of the malignancy, it is not possible on clinical grounds to differentiate radiation-induced pericardial disease from pericardial reactions caused by tumors.

Recommendations for treatment: Our therapeutic approach to patients who have radiation-induced pericardial disease is predicated on their symptoms and underlying pericardial process. In patients who have cardiac tamponade (that is, dyspnea and hypotension and an echocardiographically confirmed pericardial effusion, we advise a surgically produced subxiphoid pericardial window. In patients with incapacitating effort dyspnea, fatigue or marked hepatomegaly (liver more than 16 cm in span), we advise pericardiectomy if constrictive pericarditis is confirmed by cardiac catheterization. We do *not* currently advise surgery solely on the basis of hemodynamic confirmation of constrictive pericarditis or for the presence of recurrent pleural effusions. This approach has not led to an increased morbidity from myocardial fibrosis at our center. Objective clinical and hemodynamic data in one of our patients (Case 4) who has had no substantial changes in her evaluation over a 21 month period support this approach. Further, data[8] from patients with constrictive pericarditis caused by tuberculosis do not indicate an increased risk of myocardial fibrosis if pericardiectomy is delayed. Our recommendations are at variance with those of others[9] who advise pericardiectomy soon after the hemodynamic confirmation of radiation-induced effusive constrictive or chronic constrictive pericarditis.

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Hypertrophic Obstructive Cardiomyopathy and Lentiginosis: A Little Known Neural Ectodermal Syndrome

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Eleven patients, 10 male, with classic hypertrophic obstructive cardiomyopathy and lentiginosis are described. Physical examination showed differences from the few previously reported cases in that (1) this condition was not confined to children; (2) mental retardation, sensorineural deafness and gonadal and somatic infantilism were either rare or absent; and (3) detailed family studies provided no evidence that this condition was inherited. Nine patients underwent cardiac catheterization and left ventricular angiography; all had left ventricular outflow obstruction and three had concomitant right ventricular outflow obstruction with a pressure gradient in excess of 100 mm Hg. Ten of the 11 patients were severely symptomatic, and 7, each with a left ventricular pressure gradient of more than 70 mm Hg, underwent successful septal myotomy/myectomy that resulted in marked symptomatic improvement that was maintained after long-term follow-up.

Hypertrophic obstructive cardiomyopathy has been described in association with several anomalies of neural crest tissue, such as pheochromocytoma,[1] tuberous sclerosis[2] and neurofibromatosis.[3] These associations, together with the hemodynamic changes induced by catecholamines, led to speculation that the cause of hypertrophic obstructive cardiomyopathy might lie in a disturbance of the sympathetic nerve supply to the heart. A less well known neuroectodermal association described by Moynahan and Polani[4–6]—that of hypertrophic obstructive cardiomyopathy and lentiginosis, a disorder of the pigmentary elements of the skin—seemed to lend credibility to such etiologic speculations. This syndrome, which they called "cardiomyopathic lentiginosis," occurred in children, was reported to be dominantly inherited, and was associated with sensorineural deafness, genital hypoplasia and psychic and somatic infantilism.

In this report we describe 11 patients with hypertrophic obstructive cardiomyopathy and lentiginosis who differed in the following major respects: (1) The majority were adults; (2) deafness, psychic, sexual and somatic infantilism were either rare or absent; and (3) detailed clinical and echocardiographic family studies revealed no evidence of dominant inheritance.

Patients

Of the 11 patients with hypertrophic obstructive cardiomyopathy and lentiginosis, 10 were male and 1 was female. Their ages ranged from 16 months to 69 years (mean 43 years). The diagnosis of hypertrophic obstructive cardiomyopathy was made in 9 patients with cardiac catheterization studies indicating the presence of a left ventricular outflow tract gradient at rest; in 10 patients the diagnosis was made with echocardiographic studies showing the presence of asymmetric septal hypertrophy, systolic anterior motion of the mitral valve or mid-systolic aortic valve closure.

Results

Symptoms (Table I): All but one of the 11 patients were symptomatic; 6 had central chest pain related to exertion, 5 had grade II to IV exertional dyspnea (New York Heart Association Classification[7]) and 6 had

TABLE I

Clinical Symptoms, Electrocardiograms and Chest Roentgenograms in 11 Patients

	Patients	
	n	%
Symptoms		
Chest pain	7	64
Dyspnea (NYHA class II–IV)	5	45
Near syncope (grayouts)	4	36
Syncope	2	18
Palpitations	2	18
Electrocardiogram		
Sinus rhythm	11	100
Left ventricular hypertrophy	7	64
Left axis deviation	3	27
Right ventricular hypertrophy	2	18
Biventricular hypertrophy	1	9
First degree heart block	1	9
Chest roentgenogram		
Cardiomegaly (cardiothoracic ratio >0.55)	7	64

NYHA = New York Heart Association.

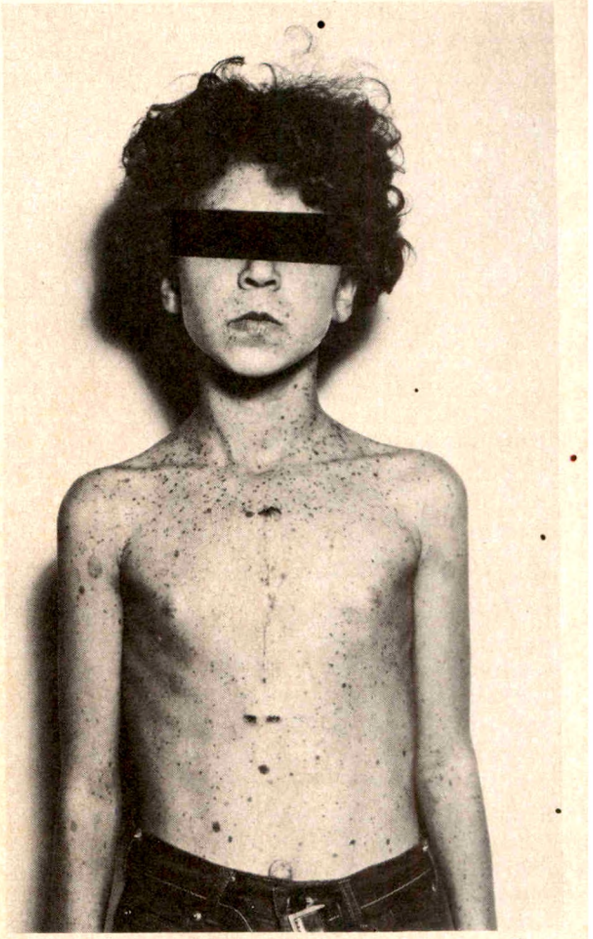

FIGURE 1. Twelve year old patient with diffuse lentiginosis and hypertrophic cardiomyopathy resulting in severe obstruction of both ventricular outflow tracts. Note the numerous dark brown spots distributed over the face, chest, trunk and back. This patient had recently undergone myotomy/myectomy successfully.

near or complete syncope. The only asymptomatic patient was referred to the Division of Cardiology for investigation of a systolic ejection murmur at the left sternal border.

Clinical examination (Table I): The most striking feature on examination, particularly in the younger patients, was the presence of lentigines, which were dark brown to black, bilaterally distributed, round or polycyclic macules appearing mainly on the trunk and limbs and sometimes on the face (Fig. 1). These lesions were diagnosed clinically by their classic appearance, and in the first seven patients they were confirmed by skin biopsy. All patients had jerky or sharp upstrokes of the carotid pulses, thrusting apical beats, and a systolic ejection murmur at the left sternal border, suggesting left ventricular outflow tract obstruction due to hypertrophic obstructive cardiomyopathy. One patient, aged 1.5 years, was at the third percentile for height and weight and had sensorineural deafness.

Chest roentgenograms revealed marked cardiomegaly (cardiothoracic ratio more than 0.55) in seven patients. Electrocardiograms were abnormal in all patients: seven had left ventricular hypertrophy, four left axis deviation, one severe right ventricular hypertrophy and one biventricular hypertrophy.

Echocardiograms (Table I): Echocardiograms were obtained in 10 patients. However, four of these were performed postoperatively and the remaining six were preoperative, but all showed systolic anterior motion of the mitral valve and asymmetric septal hypertrophy; in addition, five demonstrated mid systolic aortic valve closure.

Hemodynamics (Table II): All nine patients who had cardiac catheterization had typical hemodynamic and angiographic features of obstructive cardiomyopathy. Left ventricular end-diastolic pressure ranged from 6 to 18 mm Hg and was normal in three patients. A left ventricular outflow tract gradient at rest was present in all patients and ranged from 27 to 150 mm Hg. Three patients had, in addition, a right ventricular outflow tract gradient at rest in excess of 100 mm Hg, and one of the three had a left coronary arterial aneurysm but otherwise normal coronary arteries.

Management: Seven of the 11 patients, each with a resting left ventricular outflow tract gradient of more than 70 mm Hg and symptoms of angina or syncope, underwent septal myotomy/myectomy. There were no operative or late deaths, and all seven patients manifested marked symptomatic benefit in the postoperative follow-up period, which ranged from 1 to 12 years. Three of the four patients treated conservatively are taking propranolol, two patients have continued with propranolol postoperatively, and the asymptomatic patient is not receiving any medication.

Family history: Detailed clinical family histories of each propositus and echocardiographic examinations of five families and their close relatives failed to demonstrate a history of lentiginosis, heart disease or increased incidence of sudden death.

TABLE II

Hemodynamic Findings in Nine Cases

Case	Age (yr)	LVEDP (mm Hg)	LVOT Gradient (mm Hg)		RVOT Gradient at Rest (mm Hg)
			At Rest	After Isoproterenol	
1	32	10	74	100	...
2	69	18	30	55	...
3	20	16	75	...	...
4	35	17	60	120	...
5	9	17	150	...	120
6	55	6	95	...	...
7	20	17	27	78	...
8	1.5	9	106	...	107
9	12	15	86	...	105

LVEDP = left ventricular end-diastolic pressure; LVOT = left ventricular outflow tract; RVOT = right ventricular outflow tract.

Discussion

Initial speculations that the cause of hypertrophic obstructive cardiomyopathy was a disturbance of the sympathetic nerve supply to the heart—based on its predictable response to sympathomimetic catecholamines and its associations with neural crest anomalies—have not been substantiated. In the majority of patients, hypertrophic obstructive cardiomyopathy is transmitted by simple autosomal dominant inheritance with varying penetrance and phenotypic expression,[8] and when first reported it appeared to be no different when it was associated with lentiginosis.

Lentiginosis is a disorder of skin pigmentation that is of neural crest origin.[6] It consists of multiple brown to black macules bilaterally distributed on the trunk, limbs and face; the macules are not confined to surfaces exposed to sunlight, being present often on the palms, soles and hairy scalp. These lesions are clinically distinguishable from ephelides (freckles) because, unlike freckles, they do not darken or increase on exposure to sunlight, and they occur at or soon after birth—that is, before freckles, which appear between 4 and 6 years—and increase in number until puberty.[4,6] Skin biopsy shows characteristic histologic features, which were present in all our patients, namely (1) corrugation of the dermoepidermal junction due to invagination of the dermis by elongated rete pegs, (2) accumulation of pigment in the dermis and in the cells of the deeper and upper layers of the epidermis, and (3) increased numbers of melanocytes per unit area of skin.[6,8]

Previously reported cardiac disease in lentiginosis: Lentiginosis was first described 30 years ago as a family occurrence associated with nystagmus,[9] but no connection with cardiac disease was recognized until 1966, when Walther et al.[10] and then Matthews[11] each reported on three members of a family in two generations who had multiple lentigines, systolic murmurs, intraventricular conduction disturbances and T wave abnormalities suggesting myocardial infarction. The cause of the murmurs and electrocardiographic abnormalities, both of which were constant features in the two pedigrees, was not elucidated at the time. Subsequently, two new syndromes were postulated: cardiomyopathic lentiginosis[4,6] and leopard[12] or little leopard syndrome.[13] These two syndromes have so many features in common—(1) genital hypoplasia represented by cryptorchidism, ovarian dysgenesis and hypospadias; (2) sensorineural deafness; (3) psychic and somatic infantilism; and (4) dominant inheritance—that it seemed likely that they are one and the same disease entity. However, there was disparity as to the exact nature of the heart disease; several investigators[4,6,14–16] suggested hypertrophic obstructive cardiomyopathy; others[12,13,17] favored right ventricular outflow tract obstruction due to mild pulmonary stenosis.

Closer scrutiny of the clinical findings in the patients thus far described failed to distinguish between cardiomyopathic lentiginosis and leopard syndrome in terms of abnormal signs in the cardiovascular system. Few patients with leopard syndrome were investigated further than with right heart catheterization,[10–13] and even then the procedure did not always include angiography, and these patients were reported to have right ventricular outflow tract obstruction at the valve or subvalve level. By contrast, most patients with cardiomyopathic lentiginosis had right and left heart catheterization with biventricular angiography, which demonstrated left ventricular outflow obstruction due to hypertrophic obstructive cardiomyopathy.[6,14,16] Usually in hypertrophic obstructive cardiomyopathy, left-sided signs and appropriate electrocardiographic features dominate the clinical findings, but in patients with lentiginosis, right-sided signs may predominate, as in one of Somerville and Bonham-Carter's patients[14] and in one of our patients who had the physical findings of severe right ventricular outflow tract obstruction and extreme right ventricular hypertrophy on electrocardiography. It is thus not surprising that the clinical diagnosis of pulmonary stenosis was suggested.

Clinical features and diagnosis: With regard to the skin lesions, there was marked individual variation in the number of lentigines present (from hundreds to thousands) and, although their appearance and distribution were constant, which made differentiation from ephelides and café-au-lait spots easy, the diagnosis in some patients was obvious, but in others it was much more subtle. In all but one child, body habitus was normal and height and weight percentiles were within normal limits, and no patient had any evidence of gonadal hypoplasia. However, the one child with somatic infantilism was intellectually retarded, but this may have been related to bilateral sensorineural deafness, which occurred only in this patient. The rarity or absence of the features initially described as forming a part of the syndrome of cardiomyopathic lentiginosis[4–6] and leopard syndrome[12,13,17] is in sharp contrast to previous reports and deserves mention so that in their absence the diagnosis is not overlooked.

Our patients differed from those previously reported in several important respects: (1) There was an over-

whelming male preponderance. (2) Hitherto the association of hypertrophic obstructive cardiomyopathy and lentiginosis had not been fully documented in adults and is here described in patients of all ages from infancy to old age. (3) Clinical histories of each propositus and the pedigree and echocardiographic examination of all available close relatives of five families revealed no other family member with either hypertrophic obstructive cardiomyopathy or lentiginosis and thus showed that it is very unlikely that the mode of inheritance of this syndrome is by mendelian dominance. (4) Genital hypoplasia, deafness and psychic and somatic infantilism were rare.

Hypertrophic obstructive cardiomyopathy: We submit that in view of the large number of common features, cardiomyopathic lentiginosis and leopard syndrome are the same disease entity and that the cardiac lesion common to both is hypertrophic obstructive cardiomyopathy. In 30 percent of patients, right ventricular outflow tract obstruction is also present. The presence of lentiginosis, electrocardiographic abnormalities and a systolic murmur should raise the clinical suspicion of coexistent hypertrophic obstructive cardiomyopathy, and patients with these findings warrant full investigation and treatment. Thus, the diagnosis of cardiomyopathic lentiginosis should not be overlooked in adults in the absence of sensorineural deafness or psychic, sexual, or somatic infantilism.

Although we have seen patients with diffuse lentiginosis with no evidence of heart disease (and normal echocardiographic findings), some of these patients have heart disease other than hypertrophic cardiomyopathy. Thus, we have seen lentiginosis associated with atrial myxoma (one patient), coarctation of the aorta (one patient), aortic valve stenosis (one patient) and undefined cardiomyopathy (one patient). We believe that these examples represent chance occurrences of two distinct and separate disease entities rather than a specific relation of the type postulated for lentiginosis and hypertrophic obstructive cardiomyopathy.

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History and Physical Examination in Acute Pulmonary Embolism in Patients Without Preexisting Cardiac or Pulmonary Disease*

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The history and physical examination were assessed in 215 patients with acute pulmonary embolism uncomplicated by preexisting cardiac or pulmonary disease. The patients had been included in the Urokinase Pulmonary Embolism Trial or the Urokinase-Streptokinase Embolism Trial. Presenting syndromes were (1) circulatory collapse with shock (10 percent) or syncope (9 percent); (2) pulmonary infarction with hemoptysis (25 percent) or pleuritic pain and no hemoptysis (41 percent); (3) uncomplicated embolism characterized by dyspnea (12 percent) or nonpleuritic pain usually with tachypnea (3 percent) or deep venous thrombosis with tachypnea (0.5 percent). The most frequent symptoms were dyspnea (84 percent), pleuritic pain (74 percent), apprehension (63 percent) and cough (50 percent). Hemoptysis occurred in only 28 percent. Dyspnea, hemoptysis or pleuritic pain occurred separately or in combination in 94 percent. All three occurred in only 22 percent. The most frequent signs were tachypnea (respiration rate 20/min or more) (85 percent), tachycardia (heart rate 100 beats/min or more) (58 percent), accentuated pulmonary component of the second heart sound (57 percent) and rales (56 percent). Signs of deep venous thrombosis were present in only 41 percent and a pleural friction rub was present in only 18 percent. Either dyspnea or tachypnea occurred in 96 percent. Dyspnea, tachypnea or deep venous thrombosis occurred in 99 percent. As a group, the identified clinical manifestations, although nonspecific, are strongly suggestive of acute pulmonary embolism. Conversely, acute pulmonary embolism was rarely identified in the absence of dyspnea, tachypnea or deep venous thrombosis.

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An array of nonspecific abnormalities has been identified which has been shown to be suggestive of acute pulmonary embolism.[1–8] It is now well recognized that one cannot rely on the traditional symptoms of hemoptysis and pleuritic pain, which are indicative of pulmonary infarction, to diagnose acute pulmonary embolism.[1–8] How, then, can one make the diagnosis? It has been suggested[9] that by clinical means, one cannot make the diagnosis with any degree of reliability because the clinical manifestations are elusive. It was further suggested, therefore, that greater reliance should be placed on pulmonary arteriography.[9] Unfortunately, pulmonary arteriography is not without morbidity, although the risk is low.[3,10] Certainly it is expensive. Moreover, a variety of circumstances limit its diagnostic value. These include obesity, inability of the patient to lie flat or hold still and inability of the patient to hold his breath. Small emboli are difficult to detect by arteriography, and may require several injections as well as specialized techniques such as cinearteriography[11] or wedge arteriography.[12] Arteriographic abnormalities also occur in primary pulmonary disease.[13] Such abnormalities require differentiation from the abnormalities of pulmonary embolism, which, particularly with small distal emboli, require refined techniques

and still may not be possible to diagnose. The exclusion of pulmonary embolism therefore requires a procedure that itself imposes discomfort and risk on the patient.

Pulmonary arteriography is not a procedure to be employed without strong evidence that pulmonary embolism may be present. If one assumes that pulmonary arteriograms would not be obtained without a strong suspicion of pulmonary embolism, the reported high prevalence rate of negative pulmonary arteriograms (60 percent in one group,[14] 73 percent in another[9]) indicates an inability to exclude acute pulmonary embolism by clinical methods or an inability to identify patients in whom acute pulmonary embolism is likely.

Although several reports have enumerated the signs and symptoms of acute pulmonary embolism, few have described patients who are free of preexisting cardiac or pulmonary disorders.[5,6] Therefore, the clinical manifestations of acute pulmonary embolism itself, and not the manifestations of other diseases frequently associated with pulmonary embolism, may not be clear from such previous studies. In view of the opinion that pulmonary embolism is highly elusive,[9] the purpose of this study was to determine the clinical manifestations of acute pulmonary embolism in patients with no coexisting cardiac or pulmonary disease. It was hoped that syndromes of acute pulmonary embolism could be identified that would lead to a strong presumptive clinical diagnosis. The potential value of such an investigation is to improve the selection of patients for pulmonary arteriography and thereby reduce the number of false negative examinations.

Methods

Study patients: Two hundred fifteen adults without previous cardiac or pulmonary disorders were identified among the 327 patients included either in the Urokinase Pulmonary Embolism Trial[10] or in the Urokinase-Streptokinase Embolism Trial.[15] Each patient had arteriographically defined acute pulmonary embolism with symptoms for no more than 5 days before the pulmonary arteriogram. The physical findings reported were those noted when the pulmonary embolism was initially suspected.

All of the patients were 18 years of age or older. Patients were excluded from these studies of thrombolytic agents if they had a surgical procedure within 10 days of the diagnosis, had severe systemic hypertension, severe renal or hepatic insufficiency, a cerebral vascular accident within 2 months or an actively bleeding lesion in the gastrointestinal or genitourinary tract or if they were pregnant or were in the first 10 days after delivery.[10,15] Therefore, the identification of the prevalence of these predisposing factors in this experience is limited.

Assessment of severity of pulmonary embolization: The patients in the Urokinase Pulmonary Embolism Trial or in the Urokinase-Streptokinase Embolism Trial were categorized as having either massive pulmonary embolism (obstructions or filling defects involving two or more lobar arteries or the equivalent) or submassive embolism (obstruction or significant filling defect involving at least one segmental pulmonary artery but less than the equivalent of two lobar arteries).[10,15] The severity of the pulmonary embolization was assessed from the pulmonary arteriograms with use of a objective index.[16]

TABLE I

Symptoms of Acute Pulmonary Embolism

	Entire Group (n = 205–214) (%)	Submassive (n = 65–69) (%)	Massive (n = 140–145) (%)
Dyspnea	84	78	86
Pleuritic pain	74	85	67*
Apprehension	63	50	70*
Cough	50	55	48
Calf pain	39	43	36
Diaphoresis	36	20	44*
Hemoptysis	28	35	23
Nonpleuritic pain	17	13	18
Syncope	13	4	17*
Palpitation	10	3	13†
Angina	1	0	1

*,† Probability (p) values (massive versus submassive group
* <0.01, † <0.05.
n = number of patients in whom information regarding the specifi symptom was recorded.

Clinical manifestations: We evaluated the clinic manifestations in 215 patients without preexisting cardiac pulmonary disease. Specifically, patients were excluded if the had a history of myocardial infarction, angina pectori rheumatic heart disease, congestive heart failure for more tha 7 days, other heart disease, primary pulmonary disease systemic hypertension. Each of the characteristics of th history and physical examination that we report was specif cally noted in questionnaires that were completed when th patient entered the study immediately after completion of th pulmonary arteriogram. The diagnosis of deep veno thrombosis was based on clinical findings; venography was n required. The diagnosis of shock was made on the basis blood pressure and associated signs and symptoms. The fr quency of each sign and symptom refers to the percent patients who had the sign or symptom relative to the numb of patients for whom the information was recorded. Becau it was impossible from previous reports to determine th physical characteristics of patients without previous cardi or pulmonary disease, an entirely new analysis of the prima data was required for this study.

Results

Symptoms and physical signs: Dyspnea occurre in 84 percent of the patients and was the most frequer symptom of acute pulmonary embolism. Pleuritic pai apprehension and cough each occurred in at least ha of the patients (Table I). The most frequent sign acute pulmonary embolism was tachypnea (85 percen (Table II). Tachycardia (heart rate 100 beats/min more), an accentuated pulmonary component of th second heart sound, rales, and fever (temperature 37.5 C or more) each occurred in about half of the patient Deep venous thrombosis was identified in 41 percent the patients. A pleural friction rub was uncommon (1 percent). The occurrence of rales in more than half the patients indicates that their presence is a sign acute pulmonary embolism and is not necessarily du to accompanying disorders.

TABLE II

Signs of Acute Pulmonary Embolism

	Entire Group (n = 203–215) (%)	Submassive (n = 64–69) (%)	Massive (n = 139–146) (%)
Tachypnea (respiratory rate ≥ 20/min)	85	81	87
Tachycardia (heart rate ≥ 100 beats/min)	58	42	66*
Accentuated pulmonary component of second heart sound	57	47	62†
Rales	56	56	55
Fever (≥37.5° C)	50	51	50
Deep venous thrombosis	41	47	39
Pleural rub	18	26	14†
Cyanosis	18	3	24*
Hepatomegaly	10	11	10
Hepatojugular reflux	5	2	6

Symbols and abbreviations as in Table I.

Combinations of signs and symptoms were identified that assisted in assessing the likelihood of pulmonary embolism. Either dyspnea or tachypnea occurred in the vast majority of patients (96 percent). Dyspnea, tachypnea or deep venous thrombosis was present in 99 percent of patients. Acute pulmonary embolism was rarely encountered in the absence of dyspnea, tachypnea or deep venous thrombosis.

The combination of dyspnea and pleuritic pain and hemoptysis occurred in only 22 percent of patients (*Table III*). However, dyspnea and pleuritic pain were common (40 percent). Six percent of patients had no dyspnea, pleuritic pain or hemoptysis.

Presenting syndromes of acute pulmonary embolism: The presenting characteristics of these patients were divided into groups according to the most representative syndromes of acute pulmonary embolism (Table IV). These presenting syndromes are named and listed according to the most serious clinical characteristics. Thus, patients with circulatory collapse manifested by shock also may have had hemoptysis. However, those characterized as having pulmonary infarction with hemoptysis would not have had shock according to this method of classification. (1) The circulatory collapse syndromes of acute pulmonary embolism included shock, which occurred in 10 percent of patients and syncope without shock, which occurred in 9 percent. (2) The pulmonary infarction syndromes included hemoptysis with or without pleuritic pain, which occurred in 25 percent of patients, and pleuritic pain not accompanied by hemoptysis, which occurred in 41 percent of patients. (3) Uncomplicated pulmonary embolism, which was defined as acute pulmonary embolism without circulatory collapse or symptoms of pulmonary infarction, typically was characterized by dyspnea, and this syndrome occurred in 12 percent of patients. Uncomplicated pulmonary embolism characterized by nonpleuritic pain, usually with tachypnea, occurred in 3 percent of patients. One patient (0.5 percent) had symptoms of deep venous thrombosis and tachypnea without dyspnea or chest pain. The most frequent symptoms and signs that accompanied these presenting syndromes of acute pulmonary embolism are listed in Table V. Only one patient (0.5 percent) in the entire group had congestive heart failure, apparently as a result of the acute pulmonary embolism.

TABLE III

Combinations of Dyspnea, Pleuritic Pain and Hemoptysis in 215 Patients With Acute Pulmonary Embolism and No Preexisting Cardiac or Pulmonary Disease

	Patients	
	n	%
Dyspnea only	39	18
Dyspnea + pleuritic pain	87	40
Dyspnea + pleuritic pain + hemoptysis	47	22
Dyspnea + hemoptysis	4	2
Pleuritic pain	17	8
Pleuritic pain + hemoptysis	5	2
Dyspnea or hemoptysis or pleuritic pain	202	94

TABLE IV

Presenting Syndromes of Acute Pulmonary Embolism In 215 Patients With No Preexisting Cardiac or Pulmonary Disease

	Patients	
	n	%
Circulatory collapse syndrome		
Shock	21	10
Syncope	19	9
Pulmonary infarction syndrome		
Hemoptysis ± pleuritic pain	54	25
Pleuritic pain without hemoptysis	88	41
Uncomplicated embolism syndrome		
Dyspnea	26	12
Nonpleuritic pain	6	3
Deep venous thrombosis with tachypnea	1	0.5

The most severe embolism, as assessed with pulmonary arteriography, occurred in patients with shock (mean score 26.3), syncope (mean score 25.8) and patients with uncomplicated embolism characterized by dyspnea (mean score 23.0). The severity was greater in each of these groups than in patients with pulmonary infarction characterized by hemoptysis (mean score 18.2) or pleuritic pain (mean score 20.4) ($p < 0.05$, one way analysis of variance).

Predisposing factors: These were deep venous thrombosis, immobilization, operation, stroke and malignancy, one of which occurred in 76 percent of patients. Among the female patients, 85 percent had these predisposing factors, or a recent pregnancy or were taking antiovulatory agents. Obesity (weight 15 percent or more greater than ideal weight)[17] was a possible predisposing factor in 3 percent of patients. However, in these patients obesity was accompanied by some other disease such as diabetes mellitus or gout; none of the patients in whom obesity was an apparent predisposing factor were otherwise perfectly healthy and not treated with antiovulatory agents. Many patients had more than one predisposing factor, the average being

TABLE V

Most Frequent Signs and Symptoms in Various Syndromes of Acute Pulmonary Embolism

	Circulatory Collapse Syndrome		Pulmonary Infarction Syndrome		Uncomplicated Embolism Syndrome	
	Shock (%)	Syncope (%)	Hemoptysis (%)	Pleuritic Pain (%)	Dyspnea (%)	Nonpleuritic Pain or Deep Venous Thrombosis ± Tachypnea (%)
Dyspnea	71	89	91	82	100*	0*
Pleuritic pain	38	63	91	100*	0*	0*
Apprehension	71	74	63	65	58	0
Cough	33	42	81	39	42	33
Hemoptysis	10	5	100*	0*	0*	0*
Tachypnea ≥20/min	81	89	81	84	88	72
Tachycardia ≥100/min	86	58	56	49	81	29
Accentuated P_2	62	79	52	53	62	14
Rales	48	47	63	55	42	29
Fever (≥37.5°C)	43	21	58	52	42	29
Deep venous thrombosis	19	42	31	35	38	57

* The presence or absence of this manifestation helped define the syndrome.
P_2 = pulmonary component of second heart sound.

between one and two. A few patients (14 percent) had none of the commonly recognized predisposing factors. Specifically, 14 percent had no deep venous thrombosis, immobilization, operation, recent pregnancy, stroke, malignancy or obesity or were being treated with antiovulatory agents. However, only 4 percent of patients appeared to have been completely healthy before the embolism and were not taking oral contraceptive agents.

The distribution by sex was nearly equal; 57 percent were male and 43 percent were female. The ages were also equally distributed for the various syndromes of acute pulmonary embolism, with the exception of pulmonary infarction characterized by hemoptysis. The median age of the women in this group was 29.5 years, which was prominently lower than the age of men with hemoptysis (47.5 years) and of the women in the other syndrome groups.

Discussion

Although cardiac and pulmonary disease are well known predisposing factors for acute pulmonary embolism,[5] the histories of the patients in the Urokinase Pulmonary Embolism Trial and the Urokinase-Streptokinase Embolism Trial indicated that 65 percent of these patients were free of these conditions. The features of the history and physical examination in patients without preexisting cardiac or pulmonary disease are therefore relevant to the diagnosis of a large proportion of patients with acute pulmonary embolism. The information also may be applicable to the assessment of patients who have coexisting cardiac or pulmonary disease.

Advantages and limitations of study: A study such as this had advantages and disadvantages. The fortunate aspects are that a broad experience is made available through the data from these cooperative studies of thrombolytic agents. This is by far the largest group of patients with proved acute pulmonary embolism reported on whose diagnostic features were not confused by preexisting cardiac or pulmonary disease. The opportunity to identify the signs and symptoms in such a group, and particularly the opportunity to identify combinations of useful clinical features, is unique. Such specific information cannot be retrieved from the numerous reported studies.

A clear assessment of the limitations of this investigation is useful. There was no mechanism to determine the quality of the symptoms and signs enumerated. Thus, further details about important symptoms could not be determined. For example, we could identify dyspnea as the most frequent symptom. We could not determine if the patient had sudden and unexplained dyspnea, even though such as assessment would be of great value.[18]

In this study, data concerning the prevalence of predisposing factors should be considered in light of the source of the data. These data were obtained from a therapeutic trial. Several categories of patients were excluded such as those who had had an operation within 10 days before the onset of symptoms of pulmonary embolism. Such patients represent a large proportion of those who have acute pulmonary embolism. The predisposing factors enumerated are therefore biased by the exclusion of this group as well as other categories of patients. Because of these exclusions, it is possible that the prevalence of patients free of apparent predisposing factors may be exaggerated. However, it has been reported that pulmonary embolism occurs in previously healthy people.[19] Many of these otherwise healthy patients were obese, or had deep venous thrombosis, and some of the patients were pregnant.[19]

Role of electrocardiogram: The chest roentgenogram as well as the electrocardiogram (data we[20] previously reported on in about half of these patients) provide important data supplementing the signs and symptoms. In patients without preexisting cardiac or pulmonary disease, the electrocardiogram may be strongly supportive of the clinical diagnosis of acute

TABLE VI
Comparison of the Results of This Study With Signs and Symptoms Reported By Others in Patients With No Previous Cardiac or Pulmonary Disease

	20 Patients[5] (%)	35 Patients[6]* (massive embolism) (%)	215 Patients (this study) (%)
Symptoms			
Dyspnea	90	72	84
Pleuritic pain	80	37	74
Cough	45	. . .	63
Hemoptysis	40	11	28
Nonpleuritic pain	. . .	34	17
Circulatory arrest	. . .	28	19
Signs			
Tachycardia ≥ 100/min	65	97	58
Tachypnea ≥ 20/min	60†	. . .	85
Temperature >37.5° C	60‡	. . .	50
Rales	55	. . .	56
Deep venous thrombosis	50	. . .	41
Accentuated P_2	50	. . .	57
Pleural rub	20	. . .	18
Cyanosis	5	74	18
Other signs			
Chest splinting	25	. . .	. . .
S_3 gallop	15	83	28§
Neck vein distension	. . .	80	. . .

* Three patients had additional cardiac disease, but apparently none had pulmonary disease. † Respiratory rate >20/min. ‡ Temperature >37.8°C. § S_3 or S_4.

P_2 = pulmonary component of second heart sound; S_3 and S_4 = third and fourth heart sound, respectively.

pulmonary embolism. The most frequent abnormality is a nonspecific change of the S-T segment or T wave that occurs in more than 40 percent of patients with massive or submassive acute pulmonary embolism.[20] Even minor changes of the S-T segment or T wave are supportive of the diagnosis, especially when these are new findings or clear rapidly after the event. A normal electrocardiogram is uncommon in acute pulmonary embolism and is found in only 6 percent of patients with massive pulmonary embolism and in 23 percent of those with submassive embolism.[20] Complete right bundle branch block, right axis deviation, an $S_1Q_3T_3$ pattern or P pulmonale occurs in approximately one third of patients with massive or submassive pulmonary embolism.[20] Left axis deviation is found as frequently as right axis deviation in acute pulmonary embolism and therefore does not exclude the diagnosis.[20]

Role of chest roentgenogram: The chest roentgenogram is strongly suggestive of pulmonary embolism if it is normal in a severely dyspneic patient.[18] A dome of the diaphragm may be elevated. A localized radiodensity may represent pulmonary infarction, and a small effusion often accompanies this event. Large pleural effusions are rare in pulmonary embolism and suggest another disease process.[18] The most common abnormalities in the plain chest roentgenogram are pleural effusion or infiltrate, each of which occurs in slightly more than half of the patients with acute pulmonary embolism; but some of these patients also had cardiac or pulmonary disease.[21] At least two of the following—pleural effusion, infiltrate, atelectasis or an elevated hemidiaphragm—were present in 44 percent of patients with acute pulmonary embolism.[21]

Diagnostic clinical manifestations: The identified clinical manifestations are, as a group, strongly suggestive of acute pulmonary embolism. Patients with acute pulmonary embolism who are free of dyspnea, tachypnea or deep venous thrombosis are rarely identified, and whether such patients exist is uncertain. A comparison of the signs and symptoms that we report in patients without preexisting cardiac or pulmonary disease and the signs and symptoms reported by others in such patients is shown in Table VI. The higher prevalence of circulatory collapse and the lower prevalence of hemoptysis and pleuritic pain in the patients reported by Sutton et al.[6] reflect the greater severity of the pulmonary embolism in their patients.

Implications: The importance of the history and physical examination relates to the selection of patients for pulmonary arteriography. We do not propose that a definitive diagnosis should be made on the basis of the history and physical examination. However, a carefully performed and properly interpreted history and physical examination should markedly reduce the frequency of negative pulmonary arteriograms, which has been reported to be as high as 73 percent at some institutions.[9] Certainly, a definitive diagnosis should be made in each instance, and this usually can be accomplished by scintillation scans. If invasive or thrombolytic therapy is contemplated, then pulmonary arteriography is required. However, the indiscriminate use of pulmonary arteriography can lead to morbidity and frequently to an uncertain diagnosis.[18] The history and physical examination are fundamental to the diagnosis of pulmonary embolism. The signs and symptoms of acute pulmonary embolism are not so elusive that a tentative diagnosis cannot be made or rejected. Greater reliance on the clinical manifestations will improve the selection of patients for pulmonary arteriography, and may decrease the reported high frequency of negative pulmonary arteriograms.

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Bedside Recognition, Incidence and Clinical Course of Right Ventricular Infarction

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To evaluate the incidence, clinical characteristics and course of right ventricular infarction, 96 patients with an established diagnosis of acute myocardial infarction were evaluated during a 10 month study period. Of the 44 patients with acute inferior wall myocardial infarction, 16 had bedside evidence of right ventricular dysfunction. All had a positive Kussmaul's sign, and 12 had either a right ventricular third or fourth heart sound. Inspiratory elevation of right atrial and right ventricular end-diastolic pressures was documented in nine patients. Ventricular fibrillation developed in one patient and advanced atrioventricular block in three. All 16 patients survived and were alive 3 months after infarction. The hospital course and 3 month survival rate were not different from those of the usual patient with inferior wall infarction. Approximately one third of the patients with inferior wall myocardial infarction have bedside evidence of right ventricular infarction, which usually does not alter short-term prognosis.

Since the initial description of right ventricular infarction, the clinical syndrome has been recognized with increasing frequency. The clinical picture described by Cohn et al.[1] of acute inferior wall myocardial infarction with elevated systemic venous pressure, clear lungs, systemic hypotension and atrioventricular (A-V) block is well known. The diagnosis can be further documented with right heart catheterization or gated scintigraphy and technetium-99m pyrophosphate myocardial imaging.[2,3] The clinical incidence of right ventricular infarction has been estimated to vary between 3 and 8 percent of all cases of myocardial infarction,[4] whereas pathologic and radionuclide studies have found a 24 to 37 percent incidence rate of right ventricular involvement in patients with inferior myocardial infarction.[3,5] Most authors have emphasized the invasive diagnostic procedures and serious complications of right ventricular infarction. This study was undertaken to evaluate, in a prospective fashion, the bedside clinical diagnosis, incidence and course of right ventricular infarction.

Methods

Study patients: During a 10 month study period all 96 patients admitted to the Coronary Care Unit of the San Juan Veterans Administration Hospital, Puerto Rico with the diagnosis of acute myocardial infarction were screened by one of us. The diagnosis of myocardial infarction was established by the clinical picture plus the usual electrocardiographic and serum enzyme criteria (elevation of serum glutamic oxaloacetic transaminase, lactic dehydrogenase and creatine kinase). The site of infarction was determined with electrocardiographic criteria.[6] All patients were carefully examined for clinical signs of right ventricular dysfunction. Patients with acute inferior wall myocardial infarction and clinical evidence of new right ventricular dysfunction in the absence of pericardial disease, chronic pulmonary disease or chronic heart failure were considered to have right ventricular infarction.

Hemodynamic studies: Such studies were obtained in some patients as part of an on-going research protocol.[7] In the patients with clinical evidence of right

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ventricular dysfunction who underwent hemodynamic studies, pressure tracings were obtained during continual expiration and inspiration in the right atrium, right ventricle and pulmonary artery. Pressures were measured with a Swan-Ganz catheter through a Statham P23-ID pressure transducer and recorded with an American Optical two channel recorder. The patients were maintained on a cardiology ward during the rest of their hospital stay.

Follow-up: Follow-up information 3 months after the myocardial infarction was obtained from the clinical chart, by telephone or by personal interview. In approximately half of the patients (random selection), postconvalescence exercise testing was done using the standard Bruce protocol 3 months after the myocardial infarction.

Results

Incidence: During the study period, 96 men were admitted with a documented diagnosis of acute myocardial infarction. Forty-seven had anterior myocardial infarction, 44 had inferior myocardial infarction and 4 had lateral and 1 posterior myocardial infarction (Fig. 1). Sixteen patients (16 percent) demonstrated new clinical evidence of right ventricular dysfunction and were considered to have right ventricular infarction. All of these patients had acute transmural inferior wall myocardial infarction. One third (36 percent) of all patients with inferior wall myocardial infarction had clinical evidence of right ventricular dysfunction.

Clinical and hemodynamic data: The mean age of the 16 patients with right ventricular infarction was 55 years (Table I). Only 2 of the 16 had evidence of prior myocardial infarction. Nine patients had isolated inferior wall myocardial infarction and four had inferolateral and three inferoposterior infarction. Four patients had marked elevation of the central venous pressure (greater than 10 cm H_2O) by clinical estimate. All 16 patients demonstrated a positive Kussmaul's sign with distension of the jugular veins during inspiration.

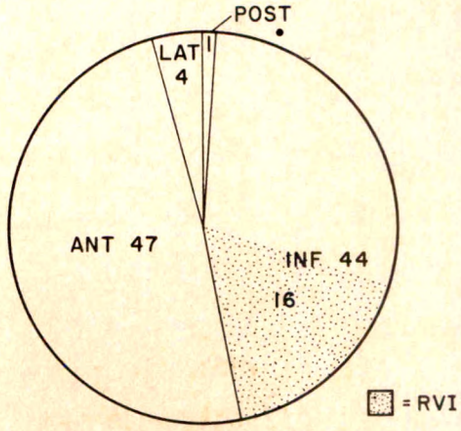

FIGURE 1. Site of acute myocardial infarction in 96 patients. **Shaded area** represents patients with acute right ventricular infarction (RVI). ANT = anterior; INF = inferior; LAT = lateral; POST = posterior.

Eleven patients had a right ventricular third heart sound and four had a right ventricular fourth heart sound. None of the patients had an audible murmur of tricuspid regurgitation. These clinical findings were present within 48 hours of admission to the coronary care unit and disappeared in all but two of the patients by the time of discharge from the hospital. Radiography was generally not helpful because only portable X-ray films were obtained; pulmonary congestion was observed in eight patients and cardiomegaly in seven.

Ten of the 16 patients with right ventricular infarction underwent right heart catheterization. Respiratory variation of right atrial and right ventricular pressures were recorded in nine patients. All nine patients demonstrated an inspiratory increase in mean right atrial pressure and in right ventricular end-diastolic pressure (Fig. 2). Mean expiratory right atrial and right ventricular end-diastolic pressure was 7.8 ± 1.2

TABLE I

Clinical Features of 16 Patients With Right Ventricular Infarction

Case	Age (yr)	Prior MI	Infarct Site	Estimated CVP (cm H_2O)	Kussmaul's Sign	Right		Compli-cations
						S_3	S_4	
1	51	No	Inf-lat	5	Yes	Yes	No	RBBB
2	51	No	Inf	7	Yes	Yes	No	None
3	54	No	Inf	6	Yes	Yes	Yes	None
4	49	Yes	Inf	12	Yes	No	Yes	VF
5	51	No	Inf-post	6	Yes	Yes	No	None
6	58	No	Inf-lat	6	Yes	Yes	Yes	RBBB
7	61	Yes	Inf	NA	Yes	Yes	No	2°AVB
8	55	No	Inf-lat	NA	Yes	No	No	None
9	61	No	Inf	12	Yes	Yes	No	None
10	58	No	Inf-post	10	Yes	No	No	None
11	53	No	Inf	7	Yes	Yes	No	None
12	58	No	Inf-lat	7	Yes	Yes	Yes	None
13	37	No	Inf	13	Yes	Yes	No	2°AVB
14	84	No	Inf	7	Yes	No	No	3°AVB
15	57	No	Inf-post	4	Yes	No	No	None
16	36	No	Inf	9	Yes	Yes	No	None

AVB = atrioventricular block; CVP = central venous pressure; Inf = inferior; lat = lateral; MI = myocardial infarction; NA = not available; post = posterior; RBBB = right bundle branch block; VF = ventricular fibrillation.

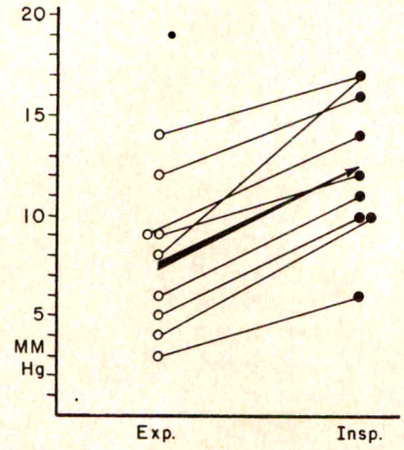

FIGURE 2. Inspiratory change in right atrial and right ventricular end-diastolic pressures in nine patients with right ventricular infarction. **Open circles** = pressure at expiration (Exp.); **closed circles** = pressure at inspiration (Insp.). **Heavy line with arrowhead** indicates mean value for the group.

mm Hg. Mean inspiratory right atrial and right ventricular end-diastolic pressure was 12.5 ± 1.2 mm Hg. The mean pulmonary arterial diastolic pressure in the group was 12.7 ± 1.1 mm Hg.

Clinical course: None of the patients exhibited clinical evidence of pericarditis, pericardial tamponade, shock or congestive heart failure during the hospital stay. Right bundle branch block developed in two patients, second degree A-V block in two and complete A-V block in one. No patient required a temporary pacemaker. Defibrillation was successful in one patient who manifested ventricular tachycardia and fibrillation. All patients survived the hospitalization and were alive 3 months after the acute myocardial infarction.

Seven patients underwent exercise testing 3 months after the myocardial infarction. The mean maximal work load achieved was 7.7 METS. This compares favorably with our previously reported value of 7 METS achieved by patients tested 12 weeks after uncomplicated convalescence from acute myocardial infarction.[8] We compared the clinical course of the 16 patients with acute right ventricular infarction with that of 14 randomly selected patients during the same study period who had had an acute inferior wall myocardial infarction without clinical evidence of right ventricular dysfunction. The incidence of complications, duration of hospitalization and 12 week survival rate were similar in both groups.

Discussion

The bedside diagnosis of right ventricular infarction has been based on the recognition of severe right ventricular dysfunction with resultant right-sided heart failure. The clinical recognition has thus been limited to cases in which right ventricular involvement has been very extensive. This may be the cause for the low reported incidence rate of clinical right ventricular infarction. Necropsy and radionuclide studies have identified a larger incidence of anatomic right ventricular infarction. This difference could be based on the fact that infarcts that involve a small amount of right ventricular muscle mass may not produce enough right ventricular dysfunction to become clinically apparent.

Response of right-sided pressures to inspiration (Kussmaul's sign): Experimental necrosis of the right ventricle has been proved to decrease the ability of the right ventricle to handle a volume load.[4] Increasing the systolic load of the right ventricle has also been proved to result in abnormal right ventricular end-diastolic pressure in patients with right coronary artery disease.[9] A maneuver that would stress the right ventricle may thus help uncover any subclinical dysfunction. The simplest bedside maneuver to stress the right ventricle is inspiration. Normally, during inspiration, there is an increase in the venous return to the right side of the heart. At the same time, pulmonary vascular impedance is decreased during inspiration, thus facilitating right ventricular emptying.[10] The inspiratory increase in venous return is so well handled by the healthy right ventricle that right ventricular end-diastolic pressure and right atrial pressure decrease. This physiologic response is altered in right ventricular infarction and may be the earliest bedside sign of right ventricular infarction. It is of interest that none of our patients with acute anterior myocardial infarction and left ventricular failure had a positive Kussmaul's sign.

Recently, Coma-Canella and Lopez-Sendon[11] also described the noncompliant nature of the right ventricle in patients with acute right ventricular infarction. This diastolic right ventricular dysfunction explains the right ventricular third and fourth heart sounds found in the majority of our patients. None of our 14 patients with inferior wall infarction and negative Kussmaul's sign exhibited a third or fourth heart sound even though four had a pulmonary wedge pressure greater than 12 mm Hg.

In some of our patients with a positive Kussmaul's sign associated with acute inferior wall myocardial infarction, right-sided hemodynamic studies were obtained. We documented elevation of the right ventricular end-diastolic pressure during inspiration. This pressure is transmitted to the right atrium and hence to the jugular venous pulse, giving the characteristic response of Kussmaul's sign. Most of our patients had a normal mean right atrial pressure, which probably reflects their minor degree of right ventricular dysfunction. None of our patients had clinical signs or symptoms of pericardial disease. Pericardial effusion was excluded by M mode echocardiography in six of the patients with right ventricular infarction. Lorell et al.[12] also emphasized this point of differential diagnosis of right ventricular infarction and pericardial disease.

Clinical course and prognosis: The clinical course of our patients with right ventricular infarction was not different from the course of a random group of patients with acute inferior wall myocardial infarction without signs of right ventricular infarction. The 3 month survival rate was 100 percent in both groups. Performance

of the patients with right ventricular infarction on exercise testing 3 months after infarction was comparable with that of our usual patient with an uncomplicated myocardial infarction. This finding indicates that right ventricular infarction may not necessarily carry a bad prognosis, in contrast to data from other studies[1,2,4] showing a large incidence of shock, A-V block and death in right ventricular infarction. This difference may again reflect the rather extensive myocardial damage needed to produce severe right ventricular failure. It appears that clinically right ventricular infarction presents a wide spectrum from a rather benign, uncomplicated entity to a catastrophic event with A-V block, shock and even death. Appropriate therapy in patients with acute right ventricular infarction and systemic hypoperfusion secondary to inadequate left ventricular filling pressure usually produces a satisfactory result.

Clinical implications: Anatomic right ventricular infarction is seen in approximately one third of patients with acute inferior myocardial infarction. Careful bedside physical diagnosis can identify these patients by demonstrating a positive Kussmaul's sign plus a right ventricular third or fourth heart sound. Generally this is a benign condition. However, in some patients such severe right ventricular failure may develop that the resultant decrease in left heart venous return will decrease left ventricular output and cause systemic hypoperfusion. In these cases, expansion of intravascular volume and use of inotropic agents usually produce hemodynamic improvement. Therapeutic interventions that decrease right-sided venous return should be carefully monitored in patients with right ventricular infarction because these interventions will compromise right ventricular output with subsequent hemodynamic deterioration.[13]

Acknowledgment

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Unstable Angina Pectoris of New Onset: A Prospective Clinical and Arteriographic Study of 75 Patients

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Seventy-five patients with unstable angina pectoris of new onset (defined as of less than 90 days' duration) were prospectively evaluated in terms of clinical and arteriographic findings. In all patients the angina was considered unstable in terms of ease of provocation of anginal attacks and frequency of occurrence of attacks. Sixty patients had significant obstruction of at least one coronary artery, whereas 15 had insignificant disease (less than 70 percent arterial narrowing) or normal coronary arteries. Thirty-one patients (52 percent) had single vessel coronary disease, 11 (18 percent) had double vessel disease and 9 (15 percent) had triple vessel disease; the remaining 9 (15 percent) had left main coronary artery disease, either alone or in association with other vessel involvement. Of the 31 patients with single vessel disease, 24 (77 percent) had stenosis of the left anterior descending artery. The patients with single vessel disease did not differ from the patients with multivessel involvement with respect to risk factors or clinical presentation.

It is concluded that patients with unstable angina of new onset have an unusually large incidence of single vessel coronary artery disease predominantly involving the left anterior descending coronary artery. Thus, these patients constitute a unique subset of patients with angina pectoris.

Unstable angina pectoris is an alarming clinical syndrome describing an accelerated pattern of ischemic chest pain, variably leading to myocardial infarction and death. Evaluation of the syndrome has been complicated by conflicting reports on the short- and long-term prognosis of affected patients.[1–12] Chahine[13] suggested that defined subgroups within the unstable angina population accounted for the variable prognoses.

One of the proposed subsets of unstable angina is that of angina of new onset or angina de novo. This clinical syndrome can be defined as the development of angina pectoris within 60 to 90 days in a patient with no previous angina. Because patients with new onset angina have so often been included in the global category of unstable angina, their particular clinical characteristics, as well as arteriographic anatomy, have not been stressed. Accordingly, this investigation was designed as a prospective study to identify the clinical manifestations and arteriographic anatomy of this subgroup.

Methods

Study patients: All patients selected for study were admitted with angina de novo to Hahnemann Medical College and Hospital between January 1977 and December 1979 and subsequently underwent cardiac catheterization within 3 months of the onset of their chest pain syndrome. A patient was included in the study group after a cardiologist other than the investigators had decided to submit the patient for cardiac catheterization. Thus, patients with angina de novo who did not undergo cardiac catheterization were excluded.

Seventy-five patients (61 men and 14 women) fulfilled the criteria for inclusion into the study. On the basis of the variables of frequency, severity, and ease of

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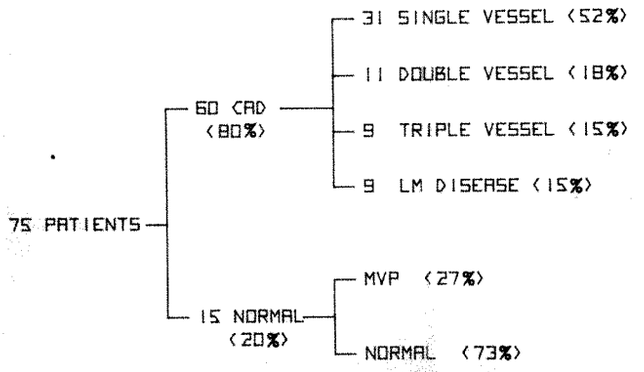

FIGURE 1. Arteriographic results in 75 patients with unstable angina pectoris of new onset. CAD = coronary artery disease; LM = left main; MVP = mitral valve prolapse.

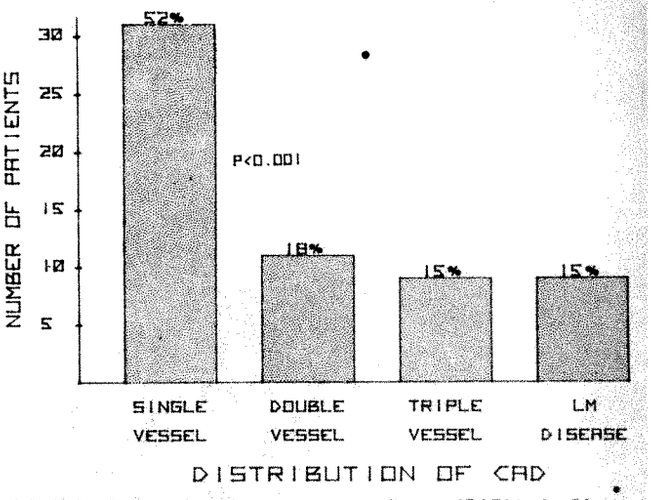

FIGURE 2. Distribution of coronary artery disease (CAD) in the 60 patients with significant obstruction. The **bars** indicate the frequency of single vessel, double vessel, triple vessel and left main (LM) coronary artery disease with percent of the group noted above.

precipitation of angina, all 75 patients were subsequently judged by us to have unstable angina, that is, to have rapidly progressive angina (type IC unstable angina using Chahine's definition[13]).

Patients with any clinical or electrocardiographic evidence of previous myocardial infarction or angina of more than 3 months' duration were excluded from the study. Similarly, patients were excluded if there was any evidence of recent infarction as diagnosed by elevation of serum creatine kinase, MB isoenzyme levels. Patients with valvular or congenital heart disease were not included in the study. All clinical histories were taken and angiographic studies reviewed by one of us in addition to the patients' own physician. All patients were entered into the study prospectively.

Risk factors: Each patient was questioned as to the presence or absence of the standard coronary risk factors. A patient was considered to be diabetic if he or she was taking insulin or an oral hypoglycemic agent or had a positive glucose tolerance test. A patient was labeled a smoker if he had at least a 20 pack-year history of cigarette smoking and had last smoked within the past 5 years. Similarly, hypertension, known hyperlipidemia and a family history of premature coronary disease were each listed as a risk factor.

Cardiac catheterization: Selective coronary arteriography was performed in nearly all patients by the Judkins technique, although a few patients with severe peripheral vascular disease underwent brachial arteriotomy using the Sones technique. The studies were performed with either a Phillips 6 inch (15.24 cm) image intensifier with videotape playback capacity or a Siemens 7.5 inch (19.05 cm) image intensifier also with video playback. The routine studies included left ventriculography in the right anterior oblique projection as well as selective left and right coronary arteriography. Views were obtained in the standard right and left anterior oblique projections as well as lateral and various sagittal oblique views so as to maximize diagnostic accuracy. The films were read by one of four arteriographers in addition to at least one investigator.

A hemodynamically significant obstruction of the coronary arteries was considered to be greater than 70 percent narrowing of luminal diameter except for the left main coronary artery where a 50 percent obstructing lesion was considered significant. Disease limited to a diagonal branch of the left anterior descending artery or a secondary marginal branch of the left circumflex artery was considered insignificant (this was present in only 1 patient). Thus, the number of vessels involved was assessed with disease of the left main coronary artery considered two vessel disease for statistical purposes. Patients with insignificant disease (less than 70 percent obstruction) of one, two or even three vessels were considered, for subgroup analysis, to have insignificant disease. In patients found to have normal coronary arteries, no maneuver to elicit coronary spasm was performed. Angiographic ventricular ejection fraction was calculated for each patient in whom a suitable end-diastolic and end-systolic frame could be measured using the area-length method.

Statistical analysis was performed using linear regression and chi-square tests.

Results

Insignificant or no coronary artery disease: Of the 75 patients studied, 60 had significant coronary artery disease. Fifteen patients had either insignificant coronary disease or entirely normal coronary arteries and were categorized together as the normal group. Of these 15, 4 patients (27 percent) had mitral valve prolapse demonstrated by ventriculography or echocardiography, or both (Fig. 1).

Significant coronary artery disease (Fig. 2): Analysis of the 60 patients with significant coronary artery disease revealed that 31 (52 percent) had single vessel disease; 11 (18 percent) had double vessel disease, 9 (15 percent) had triple vessel disease and 9 (15 percent) had disease of the left main coronary artery either alone (3 patients) or in association with other vessel involvement (6 patients). The frequency of single vessel disease differed significantly ($p < 0.001$) from that of double or triple vessel disease.

Single vessel disease: The distribution of coronary vessel involvement in the 31 patients with single vessel disease is shown in Figure 3. The incidence of disease isolated to the left anterior descending coronary artery was high. Specifically, 24 of the 31 patients (77 percent) had disease of the left anterior descending coronary artery, in contrast to 3 (10 percent) who had isolated left

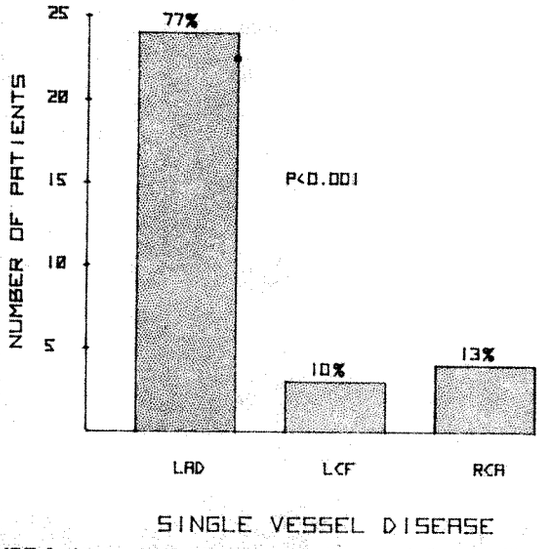

FIGURE 3. Anatomic distribution of single vessel disease. The **bars** show the percent of patients with isolated disease of the left anterior descending (LAD), left circumflex (LCF) or right coronary artery (RCA).

circumflex artery disease and 4 (13 percent) who had isolated right coronary artery disease. These values achieved statistical significance at a level of $p < 0.001$.

Degree of coronary obstruction: The coronary arterial luminal compromise in these patients was severe. Among the nine patients with involvement of the left main coronary artery, one had a 100 percent occlusion, and the mean degree of narrowing of this artery was 73 percent. Eight patients had 100 percent obstruction of the left anterior descending artery, and the mean degree of narrowing for all patients with disease of this artery was 89 percent. Similarly, 12 patients had 100 percent obstruction of the right coronary artery, and the mean degree of narrowing for all patients with disease of this artery was 92 percent. Two patients had 100 percent occlusion of the left circumflex artery, and the mean degree of narrowing of this artery was 82 percent. Of the 31 patients with significant coronary disease limited to a single vessel, that single vessel was narrowed by a mean of 91 percent.

The mean global left ventricular ejection fraction for the entire group of patients was 62 percent. For the patients with single vessel disease it was 65 percent.

Evaluation of risk factors: The total patient population was analyzed for the presence of five risk factors for coronary artery disease: smoking, hypertension, hyperlipidemia, family history of premature coronary disease, and diabetes mellitus (Fig. 4). It was not possible to separate the patients with single or multivessel coronary artery disease or disease affecting the left main coronary artery on the basis of any combination of risk factors. No correlation with any comparison of risk factors and coronary arterial anatomy could be found.

The peak incidence of single vessel disease occurred in the 5th decade (Fig. 5). There was no relation between the patients' age and the number of coronary vessels with significant obstruction.

Discussion

Not every patient with coronary heart disease initially presents with angina pectoris. In the Framingham study, only 37 percent of men and 65 percent of women had angina as the first manifestation of coronary disease.[11] The remainder presented with myocardial infarction or sudden death. These statistics may be colored by the fact that patients with rare, intermittent episodes of angina may not consult a physician about the symptom. In a population study conducted by Fulton et al.,[12] half the patients who had a myocardial infarction had had prior episodes of either new or

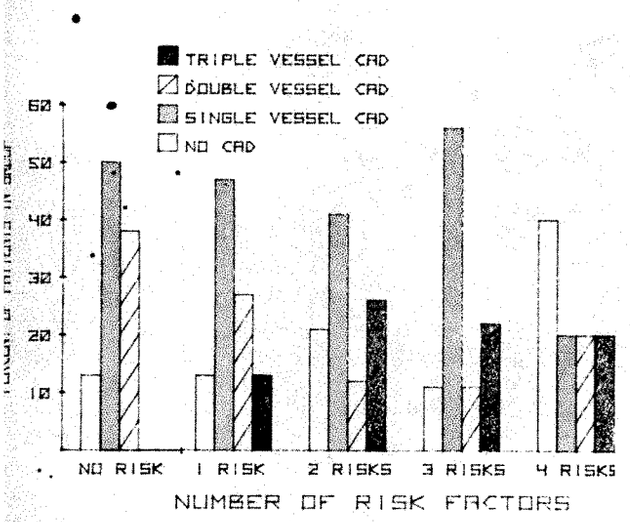

FIGURE 4. Risk factor analysis of patients with angina of new onset. The **bars** show the distribution of the patients according to their coronary anatomy versus the number of cardiac risk factors. (There was no statistical correlation.) CAD = coronary artery disease.

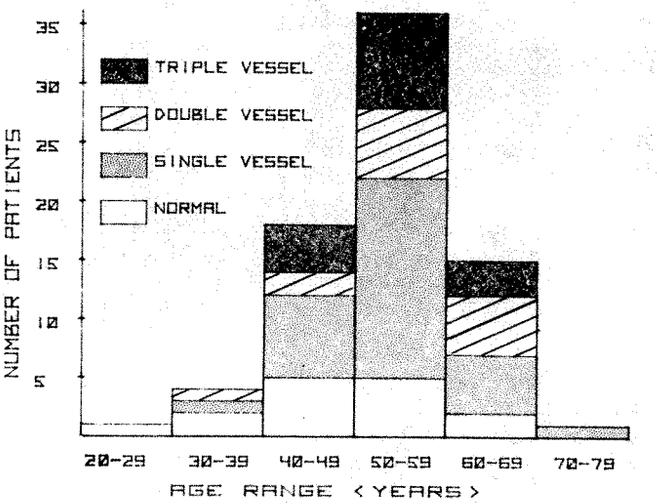

FIGURE 5. Age distribution of patients with angina of new onset. The incidence of single, double and triple coronary artery disease or no or insignificant coronary artery disease is displayed according to the patients' age by decade.

worsening angina but failed to consult a physician. Solomon et al.[14] reviewed prospectively the historical data of 100 patients admitted to the coronary care unit with myocardial infarction; 65 percent of these patients reported prodromal symptoms, mainly chest pain, within 2 months to 12 hours of infarction.

Given these facts, it would seem intuitive that physicians have long regarded rapidly progressive or unstable angina as a harbinger of myocardial infarction. Nevertheless, the population presenting with unstable angina has been difficult to define. More difficult still has been our ability to predict the eventual outcome of these patients. Thus, several investigators[1,13] have suggested analysis of the various subgroups that combine to form the population with unstable angina. In the patients with angina of recent onset constituting this report, the angina was considered unstable in all because of the increasing ease with which it was precipitated and the frequency and severity of the attacks. Indeed, it was the progressive worsening of the clinical condition that dictated the coronary arteriography. These 75 patients, therefore, represent the subgroup of patients with unstable angina de novo.

Frequency of single vessel coronary disease in new onset angina: Comparable reports of the angiographic anatomy of patients with unstable angina of new onset must be extracted from surveys of subjects classified as having unstable angina, independent of duration. One of the first clinical studies incorporating arteriography in the study of unstable angina was performed by Scanlon et al.[2] in 1973. They studied a group of 79 patients with unstable angina; 15 (19 percent) of the 79 had normal coronary arteries, 18 (23 percent) had single vessel disease, 14 (18 percent) had double vessel disease and 32 (40 percent) had disease of three or more vessels. Several later studies[3,7,8,10] confirmed that two or three vessel coronary disease could be found in more than two thirds of patients with unstable angina.

The prevalence of coronary arterial involvement changes as the duration and type of angina are categorized. Proudfit et al.[15] reported a 32 percent incidence rate of significant single vessel obstruction in patients with functional class I, II or III angina of less than 1 year's duration. Furthermore, when patients with functional class IV angina of less than 1 year's duration were examined, an approximate 40 percent incidence rate of single vessel disease was found. Likewise, in a later publication, the same group[16] described 74 patients, in a series of 601, with angina of all classes for less than 1 year. Of those 74 patients, 47 percent had significant single vessel obstruction. On analysis limited to the 21 patients with class III and IV angina, 38 percent were found to have single vessel disease. Thus, regardless of the severity of angina, the duration of the chest pain syndrome appears to be directly related to the number of coronary vessels obstructed.

These conclusions are further substantiated by the work of Lawson et al.[17] They reported on 41 patients admitted to the hospital with angina at rest whose pain persisted with hospitalization. None of the patients had an acute myocardial infarction and all underwent subsequent cardiac catheterization and coronary bypass surgery. Sixteen of the 41 patients had angina de nov as defined in our study, and 8 (50 percent) of the 16 r quired only a single bypass graft, usually to the le anterior descending artery, whereas a single graft wa performed in only 8 percent of patients with lon standing angina. In addition, when compared with p tients with long-term angina, subjects with corona insufficiency of new onset had markedly fewer collater vessels, which may have accounted for the rapid ons of symptoms.

In contrast, Douglas and King[18] found single vess disease in only 22 percent of 159 men with initial ons angina. However, it is not clear how many of these p tients had had a prior myocardial infarction or how lo the duration of the pain had been. In 22 women wi initial onset angina, cardiac catheterization reveale significant single vessel obstruction in 33 percent. Aga the characteristics of the subgroup alter the arteri graphic findings.

Our study clearly documents that the subset of p tients with unstable angina de novo is distinguished b a high percentage of persons with single vessel corona artery disease. The coronary lesions are characterist cally proximal and severely obstructed. In this serie the coronary artery most commonly involved was t left anterior descending artery.

Analysis of multiple risk factors: Our study faile to disclose any one risk factor or combination of facto that would help predict coronary arterial anatomy. addition, neither age nor sex was helpful as a predicti variable, a finding in keeping with the data of oth investigators.[18]

Ventricular function: The mean value for le ventricular ejection fraction in our patients was percent. This normal value is not unexpected becau patients with previous infarction were excluded fro the study. The routine discovery of normal left ve tricular function underscores the possibility of inte vention prior to myocardial damage.

Prognostic implications: Given the unexpected large incidence of single vessel disease in this subset patients with unstable angina, it is worthwhile to e amine the possible implications of these results on t prognosis for the population as a whole. For exampl Krauss et al.[19] studied 100 patients with coronary i sufficiency and found (1) an in-hospital mortality ra of 1 percent, and a 1 year mortality of 15 percent; (2) in-hospital infarction rate of 6 percent, with a 1 ye infarction rate of 20 percent. Gazes et al.[20] followed 140 patients with unstable angina, 27 of whom had a gina of new onset. The overall 1 year mortality rate the group was 18 percent and, thereafter, the annu attrition rate was 4 to 5 percent. However, there we no deaths and only one infarction in the first 3 mont of follow-up of patients with unstable angina of ne onset.

In contrast, Fulton et al.[12] examined 167 patients, (53 percent) of whom had unstable angina of rece onset. They found that 17 (10 percent) of the 167 h an acute coronary event (myocardial infarction sudden death) within 4 weeks and an additional ni events within the next 2 months. Similarly, Duncan

.[21] followed up 251 men, 129 (50 percent) of whom had nstable angina de novo. Twenty-eight (11 percent) of ıe 251 had a coronary event within 6 weeks and an ldditional six events occurred within the next 6 weeks. ı the latter two studies of unstable angina, the large roportion of patients with new onset angina may in art explain the high incidence rate of early coronary ents.

The distinct natural history of early onset angina has een emphasized by Short and Stowers.[22] They ana-zed the histories of patients from the onset of angina ıtil death or myocardial infarction intervened. They und a 4 percent incidence rate of coronary events ithin the 1st week after the onset of angina, a 2 per-nt/week incidence rate of events during the next 3 eeks, and a 0.6 percent/week incidence rate during the xt 2 months. Patients with an "abrupt onset" of an-na, in contrast to those with an "insidious onset," had startling 18 percent incidence rate of coronary events thin the 1st week. Clearly, then, any analysis of a pulation with unstable angina must include a detailed ronicle of the time course of the chest pain syndrome. ognosis seems to depend not only on the number of ronary vessels involved, but on the rapidity with ıich symptoms develop.

Clinical implications: This study identifies a subset patients within the category of unstable angina, namely, those with angina of recent onset or angina de novo. This group differs from the category as a whole, in that the coronary arterial lesions in more than 50 percent of the subjects may involve only a single vessel. Furthermore, the disease is apt to be proximal and severely obstructive. The desirability of performing early coronary arteriography in patients with unstable angina of recent onset should be stressed because the vascular lesions may be amenable to angioplasty[23] or aortocoronary bypass surgery.

Valid questions still exist as to the clinical pattern of these patients in terms of their propensity for early coronary events, particularly myocardial infarction. In addition, more information is needed about these patients compared with patients with angina de novo that is not unstable. Studies on the medical and surgical management of unstable angina will have to evaluate each clinical subset within an overall study group. It appears clear that the coronary anatomy and left ventricular function may vary widely depending on the clinical subset in question, thus influencing prognosis. This is particularly true of those patients with angina of new onset.

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Prognostic Importance of Anginal Symptoms in Angiographically Defined Coronary Artery Disease

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To evaluate the prognostic importance of anginal symptoms, 44 patients with angiographically defined coronary artery disease and no anginal symptoms at time of cardiac catheterization were selected from the Duke Harvard Collaborative Data Bank. They were "matched" with 127 symptomatic patients in the Data Bank who had similar coronary anatomy and ventricular function. Follow-up data indicated that the patients without anginal symptoms had a significantly better prognosis over a 7 year period than did those with symptoms: Annual mortality in the asymptomatic group was 2.7 percent compared with 5.4 percent in the group with angina ($p < 0.05$). Although the patient population was a highly selective one and the matching categories were relatively broad, these results suggest that the presence of anginal symptoms may be an important independent correlate of prognosis in patients with coronary artery disease. The absence of angina did not preclude the presence of multivessel disease and did not necessarily imply a benign prognosis, because the yearly mortality rate was nearly 5 percent in the subgroup of asymptomatic patients with three vessel disease.

Despite the large number of studies on the natural history of angiographically defined coronary artery disease, it is still not clear whether the absence of anginal symptoms (chest pain or its usual equivalents in a given patient) is of prognostic significance when symptomatic and asymptomatic persons with similar coronary anatomy and ventricular function are compared. Two approaches are possible in obtaining such data. One approach involves a prospective evaluation of patients with and without symptoms who have undergone coronary arteriography. A second, retrospective, approach compares prognosis by using a data bank that matches patients with respect to selected variables. This data bank type of retrospective analysis for patients with coronary artery disease was introduced at Duke University Medical Center,[1,2] and has also been utilized at the University of Washington.[3]

In this study, we used the Duke-Harvard Collaborative Coronary Artery Disease Data Bank to compare the subsequent survival of patients with and without anginal symptoms at time of coronary arteriography. (Because of the small number of asymptomatic patients treated surgically, only nonsurgically treated patients were considered in this report.) The asymptomatic group included apparently totally asymptomatic persons as well as patients who had been symptom-free after a myocardial infarction. Each of the patients in the asymptomatic group was matched by computer with one to three similar patients with anginal symptoms at the time of coronary arteriography.

Methods

The coronary artery disease data bank: The Coronary Artery Disease Data Bank was established at the Duke University Medical Center in 1969. Specific baseline information concerning patients' history, physical examination, chest

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roentgenogram, resting and exercise electrocardiograms and cardiac catheterization findings were acquired prospectively and stored in a computerized system that has previously been described in detail.[1,2] In 1976, the Peter Bent Brigham Hospital (with the Harvard Medical School and Harvard School of Public Health) began its own data bank as part of a joint effort with Duke. The patients selected for the present study are drawn from the Duke-Harvard Collaborative Data Bank.

Selection criteria for patients: Because the purpose of the study was specifically to evaluate the prognostic importance of anginal symptoms, patients with signs or symptoms of congestive heart failure were excluded from consideration, as were patients presenting with severe ventricular arrhythmias. A total of 44 nonsurgically treated patients who were free of anginal symptoms at the time of cardiac catheterization and had at least 75 percent stenosis of luminal diameter of one or more major coronary arteries were selected for the asymptomatic group. They constituted all such patients in the data bank, and were each individually matched with up to three similar nonsurgically treated patients with anginal symptoms. Thirty-nine of the 44 asymptomatic patients were drawn from the Duke coronary artery disease data bank, and five from the Peter Bent Brigham Hospital coronary artery disease data bank.

The symptomatic group totaled 127 patients. These patients were selected for medical rather than surgical therapy, on the recommendations of their individual physicians. Whether this selection process may have biased the results of the study are commented on at length in the Discussion section.) One hundred seventeen of the 127 symptomatic patients were drawn from the Duke experience, and the remaining 10 from the Peter Bent Brigham experience. The remainder of this section discusses aspects of the matching.

Five variables that reflected coronary anatomy and ventricular function were selected for matching: (1) the number of major coronary arteries with at least 75 percent stenosis (one, two or three); (2) left ventricular contraction pattern (because not all patients had volumetric analyses, qualitative measurements were used: normal, abnormal but not diffusely abnormal, or diffusely abnormal); (3) arteriovenous oxygen difference (3 to 4, 4 to 5, 5 to 6, 6 to 7, or greater than 7 volumes percent); (4) left ventricular end-diastolic pressure (0 to 10, 10 to 20, 20 to 30, or greater than 30 mm Hg); (5) number of prior myocardial infarctions (0, 1, 2, 3, or more). All patients were exactly matched for variables 1 and 2. For the other variables, a nearest available match was obtained using a version of the nearest available matching algorithm.[4] If several matches were of equal quality, then the match with the nearest year of catheterization to the asymptomatic patients was used. All 39 asymptomatic Duke patients were matched with 3 symptomatic Duke patients to ensure a large enough data base for comparative purposes. The smaller size of the Harvard data bank did not always permit this 3:1 ratio. Thus, only two of the five asymptomatic patients were matched with three symptomatic patients, one asymptomatic patient was matched with two symptomatic patients, and the remaining two asymptomatic patients could each only be matched with one asymptomatic patient. Because the experiences of both institutions were combined for the life table approach, this slight imbalance had no effect on the statistics defined later and had negligible effects on the resulting survival curves.

To ensure that the results of the survival analysis were not influenced by descriptors that were not selected to be matched by the computer, the asymptomatic and symptomatic patients were also compared for frequency of several other variables. These included prevalence of left main coronary arterial stenosis, left anterior descending arterial stenosis, mean age, prevalence of male sex, prevalence of diabetes mellitus and hypertension, frequency of anterior myocardial infarction and frequency of positive exercise tests. Other factors considered were month and year of entry into the study and time from myocardial infarction (where applicable) to entry in the study.

Statistical analysis: The commonly used Mantel test[5] for comparing stratified life tables was employed in this study. The test, a particular case of the Cox proportional hazards model,[6] is closely related to work by Mantel and Haenszel[7] and Cox[8]; it is described in detail in the Appendix.

The relatively small number of patients in the subgroups with one, two and three vessel disease did not permit meaningful prognostic comparisons. Based on Miettinen's formula 5.5 for a two-tailed 0.5 level test,[9] the probability of detecting a 5 percent difference in annual mortality with the entire sample was approximately 90 percent, but in a subgroup of half the sample, this probability fell to approximately 66 percent and with a subgroup one third of the sample, the probability was approximately 50 percent.

The chi-square test was used to compare the frequency of various clinical variables listed in Table I, with the exception of mean age, which was compared with use of an unpaired *t* test. The unpaired *t* test was also used to compare time from infarction to entry in the study.

TABLE I

Clinical and Angiographic Findings in Study Patients With and Without Anginal Symptoms

	Without Anginal Symptoms (n = 44)	With Anginal Symptoms (n = 127)
Mean age	47.6	49.0
Male sex	41 (93%)	107 (84%)
Diabetes	2 (4%)	8 (6%)
Hypertension	13 (29%)	27 (21%)
Diagnostic Q waves in electrocardiogram	23 (53%)	76 (60%)
Positive exercise test	17/31 (55%)	48/96 (50%)
Two vessel disease	13 (30%)	38 (30%)
Three vessel disease	18 (40%)	51 (40%)
Left main coronary arterial stenosis	0	0
Left anterior descending arterial stenosis	36 (82%)	91 (72%)
Totally occluded vessels	12 (27%)	34 (27%)
Abnormal left ventricular contraction pattern	32 (73%)	95 (75%)
Left ventricular end-diastolic pressure > 18 mm Hg	8 (18%)	18 (14%)
Arteriovenous oxygen difference > 5.5 volumes percent	9 (21%)	23 (18%)

Results

Clinical and angiographic findings in the asymptomatic patients: The major reason for cardiac catheterization in the 44 asymptomatic patients was prior myocardial infarction (32 patients). Thirty of these 32 patients were pain-free for at least 2 months before the catheterization. Nineteen of the 32 had treadmill exercise tests; 7 tests were positive by electrocardiographic criteria (1 mm or greater S-T segment depression), al-

TABLE II

Prognosis in Study Patients With and Without Anginal Symptoms

	Without Anginal Symptoms				With Anginal Symptoms			
	At Risk	Deaths*	Survival	SE	At Risk	Deaths	Survival	SE
6 months	44	0	1.000	—	127	9	0.929	0.023
1 year	44	1	0.977	0.022	114	4	0.897	0.027
2 years	34	0	0.977	0.022	103	2	0.879	0.029
3 years	29	1	0.944	0.040	90	5	0.830	0.035
4 years	22	0	0.944	0.040	73	4	0.785	0.040
5 years	17	1	0.888	0.065	52	3	0.740	0.045
6 years	12	1	0.814	0.093	33	1	0.717	0.049
7 years	5	0	0.814	0.093	21	3	0.615	0.069

* Deaths during the specific interval.
SE = standard error.

though the test did not induce angina; the remaining 12 tests were negative or nondiagnostic (no S-T segment depression and less than 85 percent of predicted heart rate achieved). The other major reason for cardiac catheterization was a positive exercise test (10 patients); the remaining 2 patients had an abnormal resting electrocardiogram. Only 3 of the 44 patients were taking cardiac medications (propranolol by 2 and propranolol and nitrates by another). These three patients had had a prior myocardial infarction and, although asymptomatic for at least several weeks after the infarction, were given these medications for prophylactic reasons by their physicians.

Table I lists other relevant clinical and angiographic findings in this group. The mean age was just under 50 years; men predominated; diabetes mellitus was uncommon; more than half the patients undergoing exercise tests had an ischemic response; stenosis of the left anterior descending artery was very common, but there were no patients with stenosis of the left main coronary artery; left ventricular asynergy was also common. The median time of entry was January 1974 for the symptomatic group and March 1975 for the asymptomatic group. No patients entered the study before 1970. The time from infarction to entry in the study (where applicable) was 27.8 months ± 6.4 (mean ± standard error of the mean) in the asymptomatic group and 33.4 months ± 4.5 in the symptomatic group (p = not significant [NS]).

Clinical and angiographic findings in the symptomatic patients: The 127 patients in the symptomatic group were all taking propranolol or nitrates, or both. Although the degree of symptoms varied considerably, less than 10 percent were considered as having unstable angina at time of catheterization. When the relevant clinical and angiographic findings in this group of patients were compared with those of the asymptomatic group, no significant differences were observed (Table I).

Prognosis in patients with and without anginal symptoms: Table II depicts the 7 year comparative survival statistics for the total group of 171 patients with and without symptoms. Only 2 of the 31 deaths were due

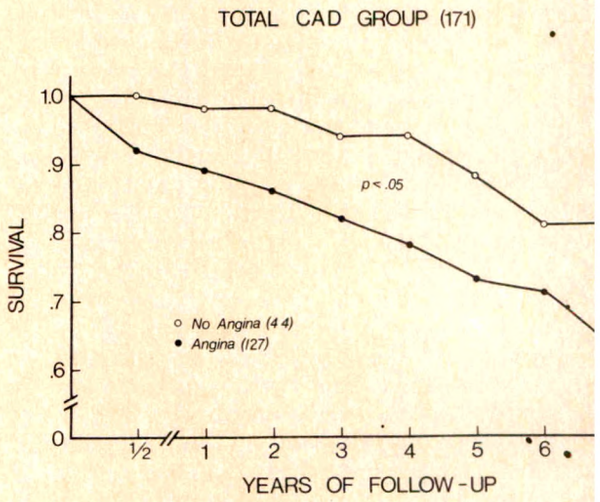

FIGURE 1. Survival curves (based on data in Table II) for 44 patie without anginal symptoms and 127 matched patients with angi symptoms.

to noncardiac causes. Figure 1 depicts the resulti survival curves. The mean follow-up time was 3.9 yea in the symptomatic group and 3.6 years in the asym tomatic group (p = NS).

There was an 81 percent survival rate for the to asymptomatic group at 7 years (yearly mortality percent) compared with a 62 percent survival rate the symptomatic group (yearly mortality 5.4 percen The worst prognosis, as expected, was in the subgro with three vessel disease (4.7 versus 8.7 percent in t symptomatic group). The survival curve for the over group was significantly better in the asymptomatic th in the symptomatic patients (p <0.05*).

Two of the four patients in the asymptomatic gro who died had anginal symptoms at least 6 months b fore their death (all four were in the subgroup with pr myocardial infarction). In general, development of a

* Mantel-Haenszel statistic 4.43 on 1 degree of freedom (t tailed).

nal symptoms was uncommon in this group. At the 6 onth follow-up period, 17 percent reported symptoms, ıd by 4 years, this figure had risen to only 30 percent. ıly 1 patient in this group was eventually referred for yocardial revascularization compared with 14 patients the symptomatic group. For purposes of this study, e last follow-up period was the one immediately eceding surgery.

Discussion

Our results suggest that patients who are not taking rdiac medications and are free of anginal symptoms the time of coronary arteriography have a better ognosis than do symptomatic patients with similar nical, angiographic and hemodynamic findings. The udy cannot be construed as a true reflection of the ıtural history of asymptomatic coronary artery dis-se, however, because nearly three fourths of the study oup had sustained a prior myocardial infarction. ırthermore, we defined asymptomatic coronary artery sease on the basis of angina alone and patients with her manifestations of myocardial ischemia (such as rhythmias and congestive heart failure) were ex-ıded. Nevertheless, the study does provide important ta in an area noted for its paucity of studies. Except r a preliminary report of a study in progress at the ıtional Institutes of Health,[10] which also suggests a tter prognosis for asymptomatic patients (2 percent nual mortality rate, similar to the 2.7 percent rate in e present study), there are virtually no data available the prognostic importance of anginal symptoms in giographically defined coronary artery disease.

Prognosis in patients with silent myocardial hemia: It is important to know the effects of anginal mptoms on prognosis because asymptomatic patients undergoing coronary arteriography with increasing quency. Whether asymptomatic patients *should* be erred for coronary arteriography is irrelevant for the rposes of this study, although it is an acknowledged ıtroversial decision. The most numerous of these tients are those with prior myocardial infarctions, as lected in the present study (32 of 44 patients). Less mmon are apparently totally asymptomatic persons o are referred for coronary arteriography, usually on basis of a markedly positive exercise test.[11] (Many the patients with a prior myocardial infarction also ve a positive exercise test.) Physicians are naturally ed with the dilemma of what treatment, if any, to er these persons. One could hypothesize that silent ocardial ischemia may be related to a defective an-al warning system and these patients may even be increased risk for myocardial infarction or sudden ıth; in other words, these patients have no angina to p them from the activity that is inducing the isch-ia.[12] This is an attractive theory, but it remains un-ven, although there are data indicating that patients h silent myocardial ischemia after myocardial in-ction—as evidenced by exercise-induced S-T seg-nt depression without symptoms—have the *same* 1 r mortality rate as patients with both S-T segment depression and test-induced angina.[13] Only 17 patients without angina in this study had a positive exercise test by electrocardiographic criteria and could be considered to have silent myocardial ischemia. This number was too small for meaningful prognostic comparisons using our data bank system, and thus we could not adequately address the issue of prognosis in silent myocardial ischemia. Large numbers of asymptomatic patients with a positive exercise test (or other evidence of myocardial ischemia such as an abnormal exercise radionuclide ventriculogram) must be followed up for at least a 5 year period to provide meaningful data concerning this important subset of asymptomatic patients with coronary artery disease.

Limitations of the study: In addition to insufficient data on the subject of silent myocardial ischemia, there are other limitations to our study that must be considered in interpreting its conclusions: (1) Some of the matching categories were relatively broad. For example, quantitative ventriculographic analyses of global and regional function were not available in many of the patients, and thus assessment of ventricular function relied on commonly accepted but qualitative indexes. In addition, the only quantitative coronary arteriographic matching criterion was the presence or absence of 75 percent or greater stenosis of luminal diameter. (2) Because the spectrum of anginal pain in the symptomatic group varied considerably from mild to severe, it is probable that within the overall group are subgroups of patients with different prognoses. This is not necessarily an undesirable feature, because having such a varied group yields a more representative "mix" of symptomatic patients. (3) Finally, could bias in the decision to treat these symptomatic patients medically have influenced the results of the study? These patients were treated medically, rather than surgically, because of the preferences of their referring physicians. The motivation of these decisions is not always readily apparent from material in the Data Bank. Therefore, it is possible that in some of these patients the degree of coronary disease or myocardial dysfunction, or both, was deemed too diffuse or severe for surgery and that despite attempts to match these factors in the asymptomatic group, the survival curves were skewed in favor of the asymptomatic patients.

Although we cannot fully exclude such bias because of the relatively broad stratifying categories employed in this study, we think the effect has been minimal for the following reasons. The annual mortality rate in medically treated but "good risk" patients is reliably estimated at 4 percent,[14] whereas "poor risk" medically treated patients have a 7.6 percent yearly mortality rate[15] and patient groups with a mixture of the two have a 5.5 percent yearly mortality rate.[16] Since our yearly mortality rate (5.7 percent) was similar to this latter figure, we believe that our symptomatic group represents a fair mix of "good" and "poor risk" medically treated patients.

Clinical implications: Despite the highly selective nature of the patient population, the relatively broad

natching categories, the absence of data on silent nyocardial ischemia, and the other qualifications nentioned, the results of this study suggest that the resence of angina is an important independent factor n prognosis. Why this is so is uncertain. It may be that he extent of ischemic heart disease is greater in patients vith angina, but there is no evidence at present to upport this hypothesis. Also unproved is the hypothesis hat angina may trigger enhanced central nervous sys- em activity resulting in an increased incidence of udden death. The absence of angina does not neces- arily indicate a benign prognosis, however, because early mortality in the asymptomatic patients with hree vessel disease was nearly 5 percent. Whether rophylactic therapy (for example, with propranolol) vould improve prognosis in this subgroup is unclear, as the role of surgery in asymptomatic patients.

Acknowledgment

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APPENDIX

The Mantel-Haenszel Test for Matched Survival Data

In the past, the Mantel-Haenszel test has been applied both o matched and to stratified binary responses, and to un- natched, stratified or unstratified, survival time responses. The current study contains a trivial extension: The test has een applied to matched survival data with multiple controls. 'or completeness, this appendix reviews the theory for natched survival data with multiple controls which parallels he theory for stratified survival time responses.

Let p_{ijt} be the probability that a patient in group i (i = 1 for no pain, i = 2 for pain), and matched set j (j = 1,2, . . ., 44) dies during year t (t = 1,2,3,4,5,6,7) given that the patient is at risk (that is, observed) throughout year t. Under the logit model

$$p_{ijt} = \frac{\exp\{\alpha_i + \beta_{jt}\}}{1 + \exp\{\alpha_i + \beta_{jt}\}}$$

$$i = 1,2$$
$$j = 1,2,. . .,44$$
$$t = 1,2,. . .,7$$

β_{jt} is the joint year and matched set effect, and $\alpha_1 - \alpha_2$ is the log relative odds of death (no pain/pain), assumed constant over years and matched sets. The Mantel-Haenszel test eliminates the β_{jt} by conditioning on the number of deaths in matched set j and year t.

Let n_{ijt} = number of patients in group i, matched set j, at risk throughout year t.

Let r_{ijt} = number of deaths in group i, matched set j, among patients at risk throughout year t.

The null hypothesis $H_0 : \alpha_1 - \alpha_2 = 0$, together with the previous logit model, implies that the pain and no pain groups have identical annual survival probabilities within matched sets. Under H_0, the conditional expectation, e, and the conditional variance, v, of the number of deaths in the no pain group are

$$e = \sum_{\substack{j,t \\ n_{+jt} \geq 1}} \frac{n_{1jt} r_{+jt}}{n_{+jt}}$$

$$v = \sum_{\substack{j,t \\ n_{+jt} \geq 2}} \frac{r_{+jt} n_{1jt} n_{2jt} (n_{+jt} - r_{+jt})}{n^2_{+jt} (n_{+jt} - 1)},$$

where a "+" subscript denotes summation over the subscript.

Under H_0, the test statistic

$$\frac{(|r_{1++} - e| - .5)^2}{v}$$

is asymptotically distributed as chi-square on 1 degree of freedom.

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Analysis of Exercise-Induced Changes in R Wave Amplitude in Asymptomatic Men With Electrocardiographic ST-T Changes at Rest

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Fifty asymptomatic men, 44 (88 percent) of whom were pilots or allied aviation personnel, were referred because of resting ST-T electrocardiographic changes indistinguishable from those of myocardial ischemia. Because of the nature of their occupations, cardiac catheterization was performed to establish the presence or absence of coronary artery disease. Exercise tests were performed and analyzed retrospectively with respect to exercise-induced changes in the S-T segment and R wave amplitude. The results were correlated with coronary angiographic and echocardiographic findings.

The 50 subjects were classified into two groups: Group I, 5 men with angiographically proved coronary artery disease, and Group II, 45 men without significant coronary arterial obstruction. Analysis of the S-T segment changes at peak exercise showed 21 subjects (42 percent) with a positive exercise test and 29 (58 percent) with a negative test. All subjects in Group I had a positive test. Sixteen subjects (35 percent) in Group II had a false positive result. Analysis of exercise-induced changes in R wave amplitude revealed that six subjects had a positive R wave response on the basis of sum of the changes in voltage in the leads measured ($\Delta\Sigma R$). Four of the six subjects had coronary artery disease and the other two were thought to have a cardiomyopathy. One subject with coronary artery disease had a negative R wave response. Echocardiography revealed five subjects with asymmetric septal hypertrophy; two of these had a positive exercise test and three a negative test on the basis of S-T segment criteria.

Thus, symptom-limited treadmill exercise testing of asymptomatic men with resting ST-T electrocardiographic changes produced a high incidence rate of false positive results when S-T segment criteria were used, whereas analysis of changes in R wave amplitude yielded only two false positive results, both in men who had evidence of other heart disease.

Asymptomatic and apparently healthy persons who show resting S-T segment and T wave changes indistinguishable from those of myocardial ischemia in a routine electrocardiogram present a common and difficult medical problem. Such persons have a low incidence rate of coronary artery disease,[1] and because treadmill exercise testing produces many false positive results, it may complicate rather than resolve the problem in many instances.

The few studies that have specifically examined patients with ST-T changes in the electrocardiogram obtained at rest in populations with a large incidence of coronary artery disease have shown that such changes at rest do not alter the sensitivity or specificity of the S-T segment response to exercise.[2–4] Unfortunately, the predictive value of exercise-induced S-T segment changes in asymptomatic patients with ST-T changes at rest is low.[1] Several studies[5] have suggested that beta receptor blockade can normalize the ST-T changes at rest seen in patients without

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heart disease.[5] Recently,[6] when similar patients with ST-T changes at rest underwent exercise testing and subsequent coronary angiography, all false positive exercise tests were eliminated when the tests were repeated after beta receptor blockade.

There is now evidence that, in populations with a large incidence of heart disease, R wave amplitude changes during exercise have sensitivity and specificity that are comparable with the S-T segment response, and that use of this criterion can reduce the number of false positive and false negative responses.[7–9] Furthermore, R wave analysis may be of use in the diagnosis of coronary artery disease in patients with left bundle branch block[10] and in patients who are taking digitalis.[9] In both these situations the value of S-T segment analysis is limited.

The aim of this project was to assess the value of exercise-induced R wave amplitude changes in asymptomatic men with resting ST-T electrocardiographic changes, to compare these changes with the S-T segment response, and to see whether the frequency of false positive S-T segment changes could be significantly reduced.

Methods

Study group: The exercise tests of 50 consecutive asymptomatic men (44 of whom were pilots or allied aviation personnel) referred between 1975 and 1979 were analyzed in retrospect. All had ST-T changes in the resting electrocardiogram performed routinely as part of the screening process for their profession. All were then referred for cardiac catheterization because the presence of heart disease, particularly coronary artery disease, had to be excluded before they could continue with their occupations. Analysis of the S-T segment response and R wave amplitude changes during exercise was made without prior knowledge of the cardiac catheterization results.

The subjects had normal physical findings and only three were taking medication, a thiazide diuretic agent in two and hydralazine for mild hypertension in one. Subjects with evidence of left ventricular hypertrophy or conduction abnormalities in the resting electrocardiogram were excluded from study.

Exercise tests: A maximal treadmill exercise test was performed according to the multistage Bruce protocol[11] with the end points being the subjects' limit of tolerance rather than a target heart rate. The three channel Avionics monitor model 3000 and computer programme P.100 was used with the CM lead system. The three precordial leads were positioned in order to include areas of maximal S-T changes seen in the resting electrocardiogram and incorporating lead CM_5 in each case.

From the analysis of the S-T segment an exercise test was considered positive if S-T depression of at least 1 mm in comparison with the tracing at rest was present in at least six consecutive beats, measured 60 ms after the J point with reference to the P-R interval irrespective of whether the S-T segment was upsloping, downsloping or horizontal. If there was resting S-T segment depression, then a further 1 mm depression with exercise was required before the test was considered positive.

R wave measurements were made from the P-Q junction to the tip of the R wave, with the patient standing at rest, as well as peak exercise. The mean value of 10 consecutive R wave measurements was taken so as to overcome the problem of respiratory variation in R wave amplitude. A test was considered positive by R wave criteria if there was either no change or an increase in R wave amplitude at peak exercise. R wave amplitude was measured in leads CM_4, CM_5 and CM_6 and the sum of the amplitudes (ΣR) was recorded, with the change in R wave amplitude designated as ΔR for the individual leads and $\Delta\Sigma R$ for the sum of the amplitude changes in all the leads.

Echocardiography: Echocardiograms were performed in all subjects, specifically seeking evidence of occult valve disease, cardiomyopathy, asymmetric septal hypertrophy, mitral valve prolapse and pericardial disease, all conditions known to produce ST-T changes at rest and during exercise. The echocardiograms were performed using a commercially available echograph (Smith-Kline Ekoline 20A) and a 2.25 megahertz transducer focused at 7.5 cm and recording on a Cambridge strip chart recorder.

Cardiac catheterization: Left heart catheterization and coronary angiography were performed in all subjects with use of the Sones or Judkins technique. Ventriculography was performed only in the 30° right anterior oblique position at 40 frames/s. Significant coronary artery disease was diagnosed when there was a diameter narrowing of 50 percent or more in the lumen of a major vessel. Left ventricular wall motion was assessed qualitatively and contraction abnormalities were noted.

Results

Electrocardiogram at rest: Changes in the S-T segment and T wave indistinguishable from those of myocardial ischemia were present at rest in all subjects studied (Fig. 1).

Cardiac catheterization: The 50 subjects were separated into two groups according to the results of coronary angiography. Group I consisted of five patients with significant coronary artery disease: one patient with single, two with double and two with triple vessel

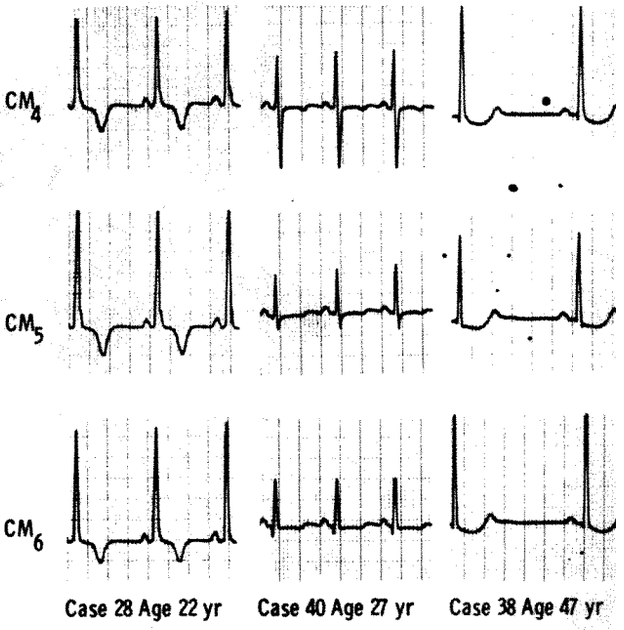

FIGURE 1. Representative changes of the S-T segment and T wave a rest.

TABLE I

Age and Heart Rates Achieved (mean ± standard deviation)

Exercise Test Result*	Age (yr)	Resting HR (beats/min)	Max HR (beats/min)
Positive (n = 21)	39.2 ± 9.6	83.7 ± 19.6	165.8 ± 18.4
Negative (n = 29)	32.7 ± 8.6	86.0 ± 15.8	173.5 ± 13.9

* S-T segment criteria.
HR = heart rate; Max = maximal.

disease. Group II consisted of 45 subjects without coronary arterial obstruction. Two of these subjects were thought to have a cardiomyopathy, with thick ventricular walls at ventriculography and increased left ventricular end diastolic pressures at rest.

Exercise testing: *S-T segment analysis:* There were 21 subjects (42 percent) who had a positive exercise test result and 29 (58 percent) a negative result. All subjects with coronary artery disease (Group I) had a positive test. Sixteen subjects from Group II had a false positive test.

Table I compares the subjects with positive and negative tests with respect to age and the resting and maximal heart rates achieved. The subjects with a positive exercise test were older, having a mean (± standard deviation) age of 39.2 ± 9.6 years compared with 32.7 ± 8.6 years in the group with a negative exercise test. The maximal heart rates achieved were 165.8 ± 18.4 beats/min for those with a positive test and 173.5 ± 13.9 beats/min for those with a negative test. The number of patients with coronary artery disease was too small to give meaningful sensitivity and specificity values.

R wave analysis: The distribution of change in R wave voltage from rest to peak exercise (ΔR) in the three leads and the sum of the change in these three leads (ΔΣR) are shown in Figure 2. On the basis of ΔΣR there were six subjects whose test was considered positive. Of these six subjects, four had coronary artery disease—one with single, one with double and two with triple vessel disease. The other two subjects with positive findings on R wave analysis were thought to have a cardiomyopathy. In 44 subjects the R wave amplitude decreased. One of these subjects had coronary artery disease (90 percent distal obstruction of a small circumflex artery, 50 percent stenosis of the right coronary artery and associated mild generalized reduction in left ventricular function). The other 43 subjects with reduced R wave amplitude had normal cardiac catheterization findings.

Analysis of lead CM_6 revealed positive results in six subjects; four of these had coronary artery disease, one probably had a hypertrophic cardiomyopathy, and one had normal cardiac findings. Analysis of lead CM_5 yielded five positive results, four in subjects with coronary artery disease and one in a subject with probable hypertrophic cardiomyopathy. Although the number of subjects with heart disease was small, it was believed that ΔΣR analysis gave the best results because the amplitude changes were greater (Fig. 2) and because all subjects with a positive test had cardiac disease.

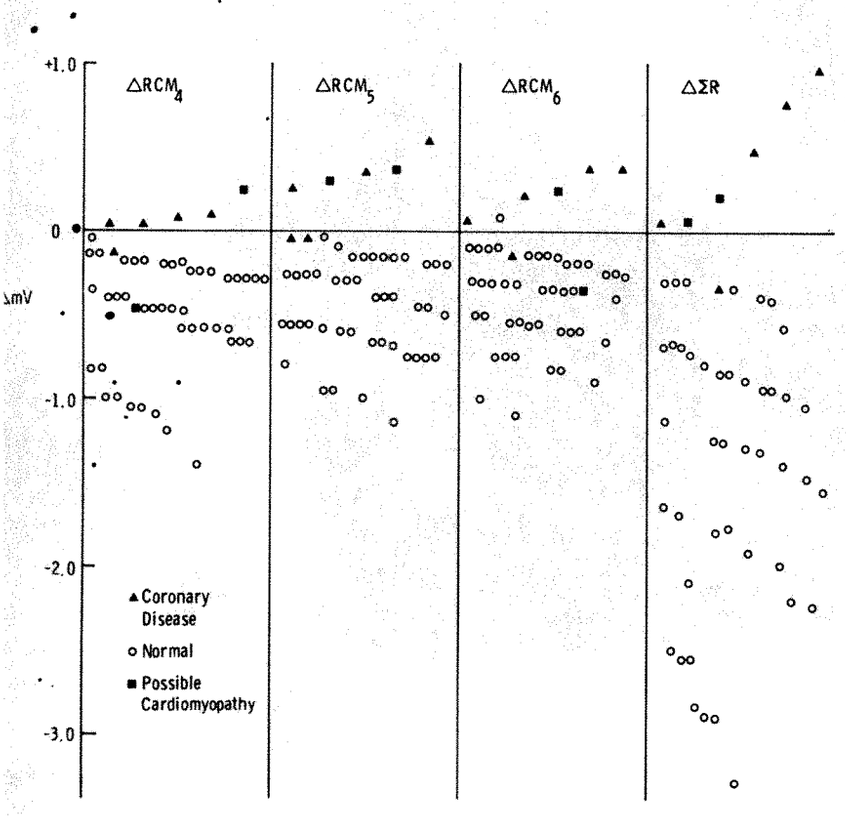

FIGURE 2. The distribution of change in voltage from rest to peak exercise in the three leads recorded and the sum of these changes. ΔmV = change in voltage (1 mV = 10 mm); ΔRCM_4, ΔRCM_5, ΔRCM_6 = change in voltage in the CM leads recorded; ΔΣR = sum of the changes in voltage in the leads recorded.

TABLE II

Age, Heart Rates Achieved and Degree of R Wave Amplitude Change (mean ± standard deviation)

R wave change	Age (yr)	Resting HR (beats/min)	Max HR (beats/min)	$\Delta\Sigma R$ (mm)	$\%\Delta\Sigma R$
Reduced R waves (n = 44)	35.1 ± 9.5	84.8 ± 17.8	171.4 ± 16.0	−14.0 ± 8.1	−24.4 ± 14.7
Increased R waves (n = 6	38.3 ± 9.8	87.6 ± 17.3	163.8 ± 19.2	+4.2 ± 3.9	+14.9 ± 19.4

$\Delta\Sigma R$ = sum of the change in R wave amplitude in the three leads measured; HR = heart rate; Max = maximal; $\%\Delta\Sigma R$ = percent change in amplitude in ΣR.

Table II compares those subjects who had an increase in R wave amplitude with those who had a decrease, when analyzing $\Delta\Sigma R$ with respect to age, heart rates achieved and degree of amplitude change. The maximal heart rate achieved was comparable in both groups (mean 163.8 ± 19.2 beats/min) in those with increased R wave amplitude and 171.4 ± 16.0 beats/min in those with decreased R wave amplitude. In the group with increased R wave amplitude only one subject had a heart rate of less than 150 beats/min. The reduction in voltage (mean −14.0 ± 8.1 mm) was greater than the increase in voltage (+4.2 ± 3.9 mm). The decrease in R wave amplitude was significant ($p < 0.01$). The decrease in R wave amplitude in the individual leads was also significant ($p < 0.01$). In those with R wave amplitude changes satisfying positive criteria, the changes were not significant in lead CM_4 ($p = 0.5$), but were significant in leads CM_5 and CM_6 and in the sum of the three leads ($\Delta\Sigma R$) ($p < 0.01$, < 0.02 and < 0.05, respectively). These statistics are acceptable considering that the definition of a positive test included those subjects with no change in R wave amplitude.

Table III shows left ventricular function data in the six subjects with positive R wave amplitude changes when analyzing $\Delta\Sigma R$. Four of the subjects had increased left ventricular end-diastolic pressure and two had segmental left ventricular wall hypokinesia.

Echocardiograms: A septal to free posterior left ventricular wall ratio of greater than 1.5 was present in five subjects. Although this isolated finding when seen in the elderly may be a normal variant,[12] all five subjects were less than 41 years old and this finding was considered abnormal. It has been reported[15] that subclinical symmetric and asymmetric septal hypertrophy (ASH) may be a cause of false positive S-T segment responses to exercise but, of the five subjects with asymmetric septal hypertrophy, two had a positive exercise test and three had a negative exercise test (on the basis of S-T segment criteria).

Discussion

Significance of S-T changes at rest in asymptomatic persons: The need to identify persons with latent coronary artery disease is nowhere better illustrated than in those whose occupations involve public safety (drivers of public service vehicles, firemen, pilots and air traffic controllers, for example). Routine electrocardiograms are now performed in such persons as well as in various screening services and as part of certain insurance assessments. Joy[14] found, when analyzing 5,217 electrocardiograms performed in civil and professional aircrew and air traffic control officers, that ST-T changes were the most frequent electrocardiographic abnormality, occurring in 3.9 percent of the electrocardiograms. The majority of these abnormalities were found in apparently healthy and asymptomatic people, illustrating that these changes in a routine electrocardiogram in an asymptomatic population present a not infrequent clinical problem.

Resting changes of the S-T segment and T wave, in the absence of heart disease, are well known and have been variously explained.[15–17] However likely these explanations are, the changes are indistinguishable from those of myocardial ischemia and the subjects often undergo treadmill exercise testing. Rifkin and Hood,[18] by applying Bayes' theorem of analysis to exercise testing, showed that the predictive value of the S-T segment response to exercise is inversely proportional to the prevalence of coronary artery disease in the population being studied. Hence, in asymptomatic patients who have a low incidence rate of disease, the predictive value of a positive test is significantly reduced and the number of false positive responses is high.[1]

TABLE III

Ventricular Function Data in the Six Subjects With Increased R Wave Amplitude

	Subjects					
	1	2	3	4	5	6
$\Delta\Sigma R$ (mm)	+7.7	+0.5	+9.9	+0.4	+4.6	+2.0
LVEDP (mm Hg)	20	20	21	10	—	13
Hypokinesia	Apical	N	Inferior	N	N	N

$\Delta\Sigma R$ = sum of the change in amplitude in the three leads measured in millimeters (1 mV = 10 mm); LVEDP = left ventricular end diastolic pressure; N = normal segmental wall motion.

False positive S-T response to exercise: In our study there was a high incidence rate of false positive S-T segment responses, although most of the causes of false positive tests had been excluded. Twenty-one subjects (42 percent) had a positive exercise test, and 16 of these were false positive tests. When the criteria for a positive test were made more stringent than those routinely used in this unit (with a further 1.5 mm depression if there was S-T segment depression in the resting electrocardiogram, and 1.5 mm depression if the S-T segment response was upsloping and measured at 80 ms after the J point) all the positive tests remained positive.

If a positive S-T segment response had been the indicator for performing cardiac catheterization, 16 subjects (76 percent) in our group with a positive exercise test would have been studied unnecessarily. Resting ST-T changes in patients with a large prevalence of coronary artery disease do not influence the predictive value of the S-T segment response to exercise.[2–4] However, when these ST-T changes were present in the asymptomatic population studied, the high incidence rate of false positive results seen was similar to that found when any asymptomatic population is screened.[1,18]

R wave responses to exercise: Analysis of amplitude changes of the R wave with exercise in populations with a large prevalence of disease has yielded comparable results with those of S-T segment analysis in several studies.[7–9] As mentioned, R wave analysis in subgroups of patients in whom the S-T segment response to exercise is of limited value has yielded encouraging results.[9,10] In the selected population we studied, coronary artery disease was correctly diagnosed in four of the five patients with this disease when R wave criteria were applied. The false positive R wave amplitude changes reported in other studies have often occurred in patients with myocardial disease with increased left ventricular end-diastolic pressure.[9,19] In keeping with these results, the two false positive R wave results in our study occurred in subjects with evidence of myocardial disease confirmed on echocardiography and ventriculography. Both subjects had increased left ventricular end diastolic pressure at rest.

The theoretical reasons for a change in R wave amplitude are many[20–22] and the few studies that have addressed themselves to establishing the reasons for the change in amplitude of the R wave during exercise have yielded varied results.[23–26] It has recently been suggested[23] that the increase in R wave amplitude after exercise in patients with coronary artery disease may be due to the inability of these patients to achieve an adequate heart rate at peak exercise. As Wolthius et al.[27] showed in normal subjects, there is a slight increase in R wave amplitude up to a heart rate of about 140 beats/min and then a fairly dramatic reduction in amplitude at higher rates; hence, if these rates are not achieved, an increase in R wave amplitude would be recorded. In our study (Table II), the heart rates achieved in those with increased R wave amplitude and in those with decreased R wave amplitude were comparable and significantly above 140 beats/min. An inadequate rate, therefore, is clearly not the reason for the increase in R wave amplitude in the group studied. In fact, the hemodynamic responses to exercise were normal in all our subjects. Whatever the reasons are for the change in R wave amplitude during exercise, our study demonstrates that the number of false positive exercise responses is significantly reduced when R wave amplitude changes rather than S-T segments are analyzed. Furthermore, all subjects who had a false positive R wave response were thought to have other heart disease. As previously shown,[6] beta adrenergic blockade may abolish the false positive S-T segment response to exercise in asymptomatic patients with ST-T wave change at rest. Our study demonstrates that, in similar subjects, analysis of exercise-induced R wave amplitude changes gives comparable results.

Clinical implications: The reliability of changes in R wave amplitude must be further studied before use of this criterion obviates the necessity for coronary angiography when ST-T changes at rest and a positive exercise test occur in patients whose occupation involves public safety. However, among asymptomatic men in other occupations with ST-T changes at rest, diminished R wave amplitude after exercise, even in the presence of a positive test based on S-T segment criteria, strongly suggests the absence of coronary artery disease, making coronary angiography unnecessary. There are many unanswered questions about this group of asymptomatic subjects with ST-T changes at rest. The key issues as to the nature of these abnormalities in the absence of cardiac disease and the natural history of these changes remain unresolved.

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Human Ventricular Refractoriness: Effects of Increasing Current

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The ventricular effective refractory period is commonly employed as a measurement of ventricular excitability. Because the current strength used to make this determination varies among laboratories, the relation of refractoriness and current was examined over a range of current strengths from 0.1 to 10 mA. Sixty determinations of refractoriness at variable current strengths were made in 40 patients using the extrastimulus technique with a rectangular pulse of 1 ms duration. These data were obtained by measuring the effective refractory period at threshold current and at 0.25 to 0.50 mA increments from threshold up to 10 mA. In these studies the drive stimulus (S_1) and extrastimulus (S_2) were kept at the same amplitude. In all patients the ventricular effective refractory period decreased as the current increased. The total decrease ranged from 8 to 100 ms (mean ± standard deviation 36.9 ± 17.1). The current strength at which the ventricular effective refractory period became fixed (that is, less than 2 ms change in ventricular effective refractory period with further increase in current strength) varied among the patients, but in all instances equaled or exceeded 1.8 mA, which in all but three patients was greater than three times threshold. The curves relating current strength and refractoriness were shifted to the left at shorter cycle lengths with no change in threshold.

These data suggest that (1) current strength-effective refractory period curves more completely characterize ventricular excitability than does a ventricular effective refractory period at single current strength; and (2) studies of drug effects, alterations of autonomic tone, or reentrant arrhythmias, which may affect or are affected by ventricular refractoriness, may be enhanced by more complete measurements of refractoriness afforded by the current strength-effective refractoriness curves.

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Determination of the ventricular effective refractory period is routinely employed as a measurement of excitability in clinical electrophysiology. The effective refractory period has been defined as the period following depolarization during which no response can be elicited by premature stimuli at some multiple of threshold. Refractory period measurements are made using the extrastimulus method, but current strengths ranging from threshold to twice diastolic threshold have been used in different laboratories.[1,2] Adrian[3] demonstrated that in excitable tissue the period of nonexcitability shortens as the strength of the applied extrastimulus is increased. This phenomenon has been observed repeatedly in intact mammalian hearts and in isolated cardiac tissues.[4–7] Therefore, the refractory period is a measurement that is meaningful only when related to the strength of the stimulus.[8]

Measurements of the current dependence of refractoriness have been used to characterize more completely the excitability of isolated cardiac tissue by expressing the refractory period as a function of the applied

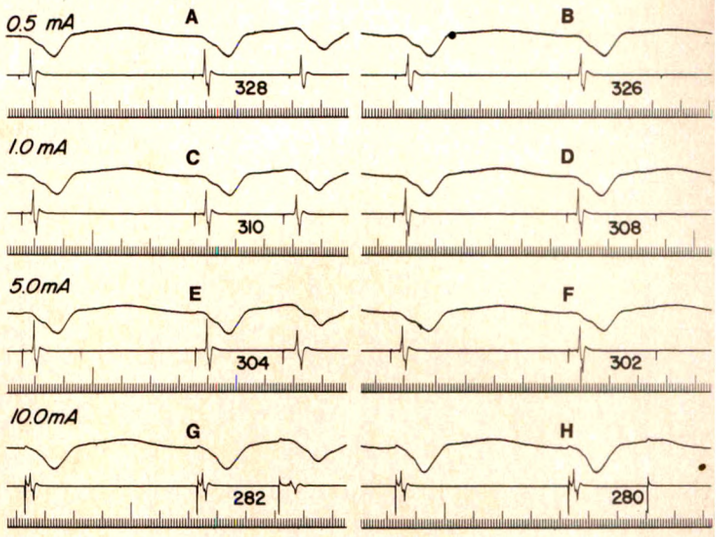

FIGURE 1. Method of measuring current-dependent changes in refractoriness. Analog records of surface lead V_1 and intracardiac electrograms from the right ventricular apex are displayed from top to bottom in each panel. In panel **A**, a premature stimulus, current strength 0.5 mA, was introduced during a basic ventricular drive of a cycle length of 600 ms, at a coupling interval of 328 ms and produced a propagated response. **B**, at the same current strength, a premature stimulus introduced at a coupling interval 2 ms shorter failed to capture the ventricle. **C**, increasing the current-strength of both the ventricular drive and the extrastimulus resulted in capture of the ventricle down to a coupling interval of 310 ms. But shortening of the coupling interval to 308 ms at the new current strength eventually leads to refractoriness (**D**). The cycle is repeated with 0.25 mA increments in current strength from threshold to 5 mA, and in 0.5 mA increments from 5 to 10 mA (**E** to **H**).

current.[9] However, similar analyses have not been done systematically in the human ventricle. Because assessment of ventricular excitability has implications for understanding the mechanisms of arrhythmias and the properties of antiarrhythmic agents, we undertook this study to characterize the relation of current strength to refractoriness in order to analyze the excitability of the human ventricle and to determine a better measure of refractoriness.

Methods

Electrophysiologic technique: The relation between ventricular effective refractory period and stimulus strength (current strength-effective refractory period curve) was studied in 40 patients, 12 women and 28 men, ranging in age from 16 to 82 years, undergoing electrophysiologic evaluation for clinical indications. In each patient tripolar and quadripolar electrode catheters (1 cm interelectrode distance) were introduced percutaneously by way of the right or left femoral or antecubital veins and positioned under fluoroscopic guidance in the high right atrium, atrioventricular (A-V) junction (His bundle recording site), coronary sinus and right ventricular apex. Stimulation was achieved with the quadripolar catheter firmly lodged at the right ventricular apex, using the distal electrode pair, while electrograms were recorded from the proximal pair. Stability was confirmed by low reproducible late diastolic thresholds and by visual observation of catheter position under fluoroscopy.

Ventricular effective refractory period determinations were made with the extrastimulus technique using bipolar stimulation, with the distal pole as cathode. Current was delivered as a rectangular impulse of 1 ms duration and variable current strength (0.2 to 10.0 mA). The intracardiac recordings were simultaneously displayed with multiple electrocardiographic leads, usually leads I, II and V_1, on an eight channel oscilloscope (Electronics for Medicine).

Data were obtained as follows: Diastolic threshold was determined by stimulating the ventricle during late diastole (more than 75 percent of the R-R interval). With use of a programmable stimulator (Bloom Associates Ltd., Inc., Narberth, Pennsylvania), progressively more premature ventricular extrastimuli (S_2) were introduced at the right ventricular apex after the eighth paced complex (S_1) of a basic drive at a cycle length of 600 ms. The S_1-S_2 interval was reduced by one to 2 ms decrements until S_2 failed to initiate a ventricular response. This interval, the effective refractory period, was determined first at diastolic threshold. Then the intensity of S_1 and S_2 was increased simultaneously in 0.25 mA increments up to 5 mA, then in 0.5 mA increments up to 10 mA. The S_1-S_2 interval was kept constant at the previously refractory interval until a current intensity was found at which S_2 again initiated a ventricular response. At this new current, the S_1-S_2 interval was decreased in 1 to 2 ms decrements until S_2 was again refractory. The current was then increased and the interval held constant until a response was initiated. This cycle was repeated up to 10 mA. Selected analog records from such a current strength-effective refractoriness curve determination are shown in Figure 1. In patients without ventriculoatrial conduction, the atrium was paced simultaneously with the ventricle to avoid intermittent ventricular capture by atrial depolarizations.

The reproducibility of the effective refractory period at any current and interval was verified by multiple (two of three) determinations before changing the current. Diastolic threshold was measured several times during the study to insure stability. The entire process was repeated at one or more additional cycle lengths in 15 patients. All data are reported as mean ± standard deviation unless otherwise specified.

Results

Effects of Changes in Current Strength

Sixty determinations of current strength-effective refractory period curves were made in 40 patients. Right ventricular threshold ranged from 0.2 to 2.5 mA (mean 0.81 ± 31). In all patients the effective refractory period of the ventricle decreased with increasing current (Fig. 2). The ventricular effective refractory period at threshold ranged from 204 to 350 ms (mean 268.3 ± 35.4), whereas that at 10 mA ranged from 180 to 294 ms

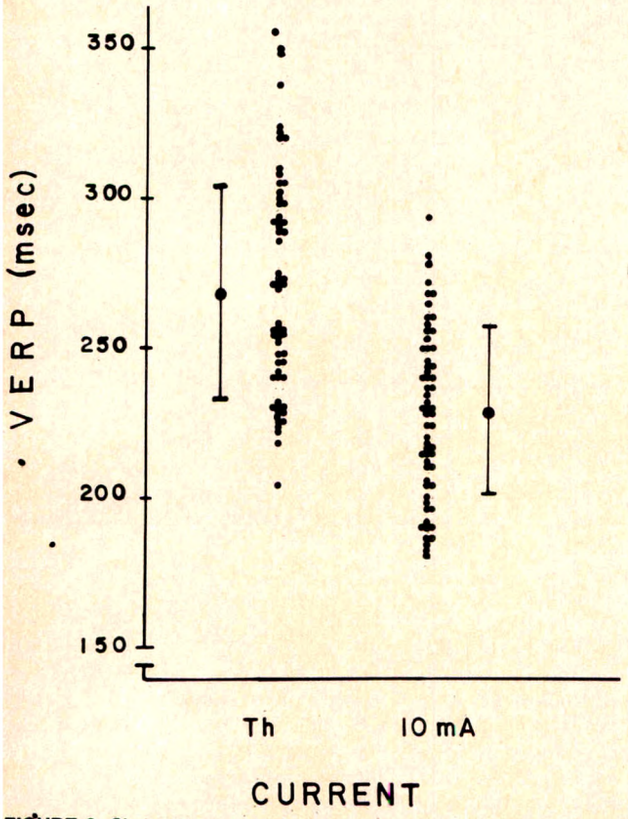

FIGURE 2. Change in ventricular effective refractory period with increasing current strength. Ventricular effective refractory periods (VERP) measured during 60 current strength-effective refractory period determinations are plotted on the ordinate versus two selected current strengths (that is, threshold [Th] and 10 mA on the **abscissa**). The mean value for all 60 curves at threshold current is significantly greater than that at 10 mA.

(mean 229.4 ± 28.2). This difference was significant ($p < 0.001$). The relation between current strength and the ventricular functional refractory period was not systematically studied in each case. In patients in whom it was examined, the functional refractory period also decreased with increasing current strength, although not to the same degree as the ventricular effective refractory period.

The relation between ventricular refractoriness and current strength was nonlinear. At low current strength (<4 mA) small increments in current (1 mA) resulted in large changes in effective refractory period (10 to 50 ms), whereas at higher current strengths (>6 mA) the change in effective refractory period of the ventricle with a 1 mA increment in current was small, and the curve became steep. A typical curve relating effective refractory period to current strength is shown in Figure 3.

The total change in the effective refractory period of the ventricle with increasing current, from threshold to 10 mA, ranged between 8 and 100 ms (mean 36.8 ± 16.1). The total change in ventricular effective refractory period with increasing current from twice threshold to 10 mA was 27.1 ± 10.9. In three patients with a high diastolic threshold (not attributable to unstable catheter position) (2.0 to 2.5 mA), the total change in refractory period was only 8 to 10 ms. However, in the majority of patients (72 percent) the total change in refractory period was 20 to 40 ms (Fig. 4).

The current strength at which the curve became steep, defined as the current beyond which no more than a 2 ms change in ventricular refractory period occurred, averaged 6.73 ± 1.9 mA. In Figure 5 threshold current is compared with the current at which the curve

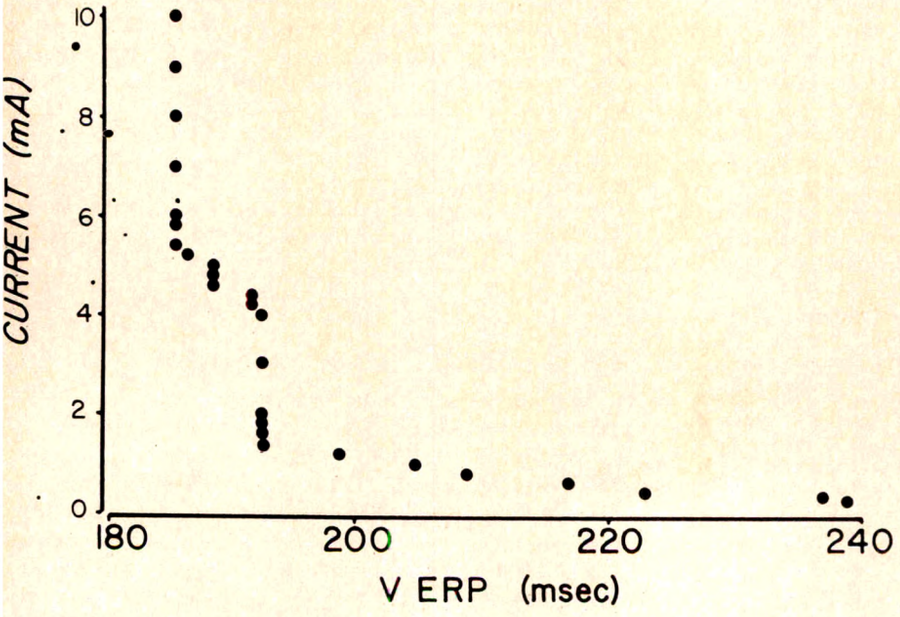

FIGURE 3. Typical curve relating current strength and ventricular refractoriness. The ventricular effective refractory period (VERP) at a given current strength (**abscissa**) is plotted against the current strength of the stimuli (**ordinate**). At diastolic threshold, 0.35 mA, the ventricular effective refraction period is 238 ms. With increases in stimulus current there is a gradual decrease in the effective refractory period until it becomes fixed at 185 ms, despite further increases in current from 5 to 10 mA.

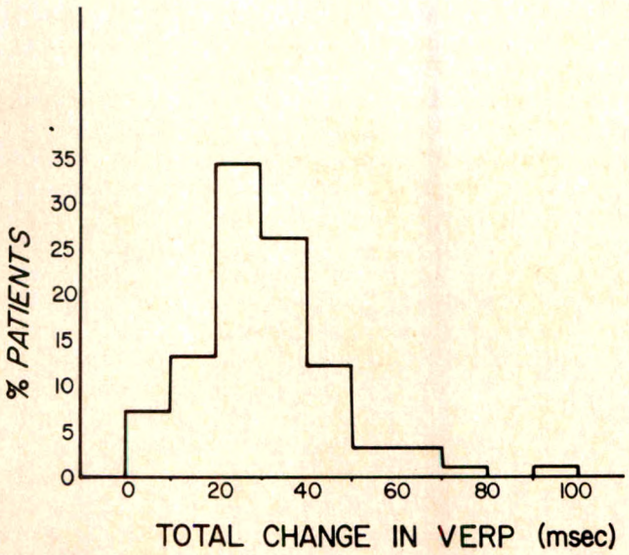

FIGURE 4. Analysis of the total change in ventricular effective refractory period (VERP) with increasing current. The total change in ventricular effective refractory period with increasing current from threshold to 10 mA (**abscissa**) is plotted against the percent of patients demonstrating such a total change. In three patients (7 percent) with a high diastolic threshold, the total change in ventricular effective refractory period was less than 10 ms; in 72 percent of the patients the total change with increasing current was between 20 and 40 ms.

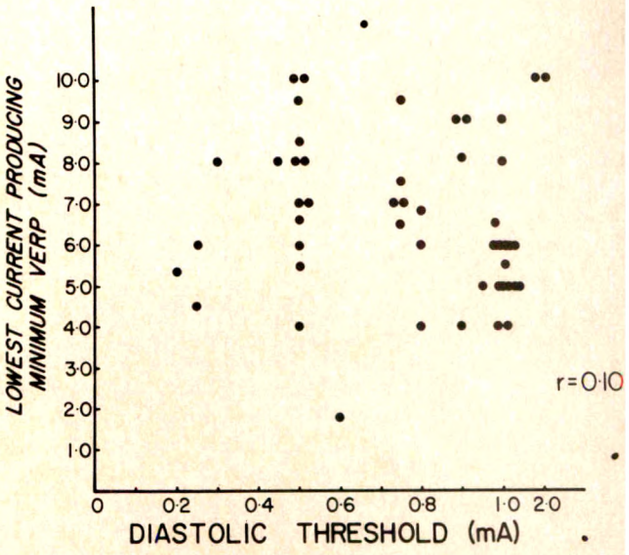

FIGURE 5. Relation of the current strength at which the ventricular effective refractory period became fixed to diastolic threshold. Diastolic threshold in ms (**abscissa**) is plotted against the current strength in mA at which the ventricular effective refractory period became fixed (**ordinate**). By linear regression analysis there is no correlation between these two variables (r = 1.0). In all but one determination, the current strength associated with the fixed minimal ventricular effective refractory period was greater than 4.0 mA.

became steep. This plot demonstrates that there was marked scatter in the values of the current required to reach the steep portion of the current strength-effective refractory period curve. Moreover, with any diastolic threshold the current at the onset of the steep portion of the curve was quite variable. There was no relation between threshold current and the current at which the curve became steep. In all but one patient the onset of the steep portion of the curve occurred at 4 mA or greater, and was greater than three times threshold in all but the two patients whose effective refractory period changed less than 10 ms. In these two patients (three curves) with a threshold of 2.5 mA, the steep part of the curves occurred at 6.5 or 7.0 mA. In 30 patients the change in the effective refractory period of the ventricle was less than or equal to 2 ms as current was increased from 7 to 10 mA, whereas the change in effective refractory period exceeded 25 ms as current was increased from threshold to 7 mA. The effect of stimulus strengths greater than 10 mA was not determined.

Effect of Changes in Cycle Length

The effect of cycle length on this relation between current strength and refractoriness was studied in 15 patients. Current strength-effective refractory period curves were measured at two drive cycle lengths (600 and 400 ms) in 15 patients and at a third drive cycle length (800 ms) in 5 of the 15. Shortening the basic drive cycle length from 800 to 600 or from 600 to 400 ms did not alter the shape of the current strength-refractory period curve. An example for a change in cycle length from 600 to 400 ms is shown in Figure 6. Although late diastolic threshold was unchanged at the shorter cycle lengths, refractory periods were shorter at each current strength; that is, the curves were shifted to the left. Thus, at a cycle length of 800 ms the effective refractory period at threshold ranged from 305 to 350 ms (mean 327.5 ± 31.8) and at 10 mA ranged from 260 to 281 ms (mean 270.5 ± 14.9). At a cycle length of 600 ms the effective refractory period at threshold and 10 mA ranged, respectively, from 245 to 305 ms (mean 269.7 ± 29.2) and from 212 to 265 ms (mean 237.8 ± 18.2), whereas at a cycle length of 400 ms the ventricular effective refractory period at threshold and 10 mA ranged, respectively, from 218 to 258 ms (mean 233 ± 15.1) and from 190 to 231 ms (mean 202.1 ± 14.9). The differences in the mean effective refractory period at a given current strength for each cycle length were statistically significant ($p < 0.001$). However, the total change in effective refractory period with increasing current strength was essentially unaltered when determined at the three cycle lengths, averaging 42.8 ± 19.5 ms at a cycle length of 800 ms, 38.1 ± 8 ms at a cycle length of 600 ms and 31.4 ± 7 ms at a cycle length of 400 ms ($p > 0.05$).

Discussion

The excitability of cardiac muscle, as determined by applied extrinsic stimuli, has been evaluated in intact mammalian hearts and isolated heart muscle using the strength-interval relation.[4,6,10] As stimulation occurs earlier in the cardiac cycle, more current is required to

initiate a response. The curve relating current strength and refractoriness becomes steep at a specific coupling interval that is related to the absolute refractory period (that is, the period during which no stimulus strength will excite the tissue). These curves are reproducible in different species and have the characteristic that at low current strengths small changes in current cause large changes in refractory period, whereas at high current strengths changes in refractory period with similar changes in current approach 0. The relation between stimulus strength and refractory period is therefore nonlinear.

This study has evaluated the effects of current intensity on ventricular refractoriness in the human ventricle. We have shown that the characteristic nonlinearity of the relation between current strength and refractoriness holds in the human ventricle using bipolar stimuli of 1 ms duration, delivered through a transvenous intracardiac electrode catheter with an interelectrode distance of 1 cm. The shape of the current strength-effective refractory period curve is in some respects similar to the strength-interval curves observed in intact mammalian hearts and isolated cardiac tissue.[4,5,10]

Moreover, cycle length-dependent effects on the current strength-effective refractory period relation have been demonstrated. Decreased cycle length has been shown to be associated with a decreased ventricular effective refractory period in the human heart at twice diastolic threshold.[1,2] Our results extend this observation over a range of current strengths. In the present study, as cycle length was shortened from 800 to 600 to 400 ms, the ventricular effective refractory period decreased at comparable current strengths. Although threshold current remained unchanged as did the general configuration of the curve, the steep portion of the curve shifted leftward. This indicates that the rate of recovery of excitability occurs earlier at shorter cycle lengths, and may in part be related to shortening of the action potential associated with decreased cycle lengths.

Importance to clinical electrophysiology: Our results have implications for clinical electrophysiology. The ventricular effective refractory period is a variable that is used to define the functional characteristics of the ventricle. We have shown that the measured ventricular effective refractory period in man varies in a predictable way with current strength, and we believe that this variable could be more completely and precisely characterized by measuring the current strength-effective refractory period curve. The determination of the effective refractory period at multiple current strengths, rather than at one current strength probably provides a more accurate measure of excitability[8] because a change in excitability at current strengths higher or lower than that used for testing would otherwise go undetected.

More precise determination of ventricular refractoriness would be important in studies of the effects of drugs[11] or alterations in autonomic tone[12] on basic electrical characteristics of the ventricle, such as excitability. In addition, since the ability to initiate or terminate reentrant arrhythmias by programmed stimulation is dependent on the refractoriness of the limbs of the reentrant circuit,[13–15] studies of such arrhythmias would be facilitated by precise measurements of tissue refractoriness of the circuit. In this regard determination of the behavior of the ventricular functional refractory period as well as the effective refractory period with current strength is pertinent, since the functional refractory period determines the shortest ventricular coupling interval that can be achieved to influence the reentrant circuit.

Utility of the modified strength-interval relation: Our data suggest that if the effective refractory period of the ventricle is determined at a single current

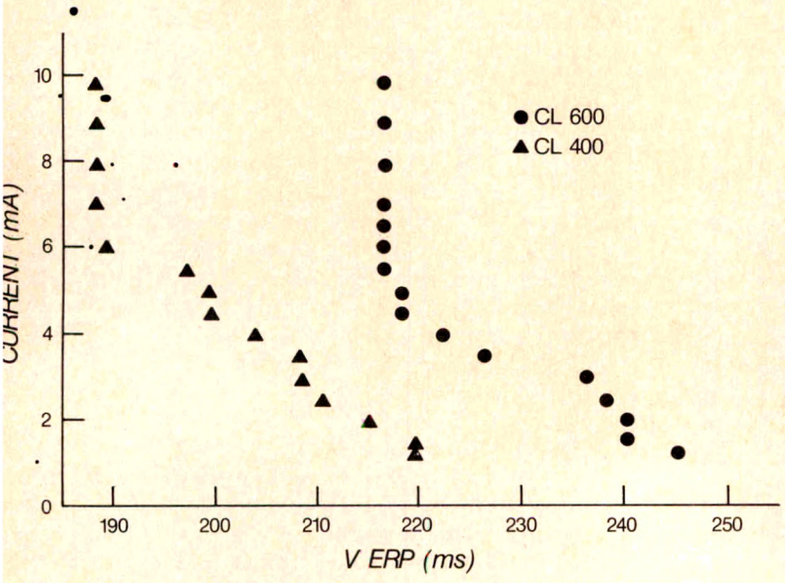

FIGURE 6. Effect of cycle length on the relation of ventricular refractoriness and current. Curves relating ventricular effective refractory period (VERP), and current strength of applied stimuli, measured during refractory period determinations at two different drive cycle lengths are plotted as in Figure 5. **Closed circles** represent measurements made at a basic cycle length (CL) of 600 ms and **closed triangles** those made at a basic cycle length of 400 ms. At the shorter cycle length late diastolic threshold is unchanged. The ventricular effective refractory period at all current strengths is decreased at the shorter cycle length, causing the curve to be shifted to the left. However, the curves become steep at similar current strengths (5.5 mA at 600 ms and 6.0 mA at 400 ms).

strength, it would be more appropriate to do so at a current strength at which changes in current produced minimal changes in the effective refractory period, that is, at the steep portion of the curve. As in the strength-interval relation, the onset of the steep portion of the curve reflects the end of the ventricular relative refractory period and the onset of the irresponsive interval or absolute refractory period. Although the current strength at which this occurs varies considerably from patient to patient, our data show that one can generally predict that the steep portion of the curve will occur at current intensities between 7 to 10 mA.

Relation to isolated tissue studies: Current dependence of refractoriness has not been extensively studied in human beings. Gettes et al.[16] measured strength-interval relations in the right ventricle of people with A-V block requiring pacemakers, and showed that it is affected by changing potassium and calcium concentration in the blood. However, most of the information on ventricular excitability has been gathered from mammalian hearts,[7,10] isolated cardiac tissue[4] or Purkinje fibers.[17]

The curves obtained in our study reveal the same phenomenon observed in animals, that is, the effective refractory period shortens with increasing current. However, there is a significant difference. In animal studies an interval was found at which the muscle becomes easier to excite; that is, less current is required than at longer coupling intervals. This has been referred to as a supernormal period and has been found to correlate with the so-called vulnerable period,[6] during which bursts of extrastimuli more easily induce ventricular fibrillation. Our technique does not permit observation of this phenomenon, because it requires determination of a new threshold at each coupling interval, rather than increasing current as extrastimuli are moved earlier in the cycle. Therefore, although the current strength-effective refractoriness curve as determined by our technique demonstrates current-dependent changes in refractoriness, it cannot evaluate the "supernormal" period in the human heart.

Limitations of the technique: Of necessity, refractoriness in the human heart is defined as the failure to induce a propagated response recorded by a bipolar electrode pair 1 cm away from the site of stimulation. Therefore in the intact human heart using the extrastimulus technique, one cannot distinguish between failure of a stimulus to excite the cardiac cell and failure to conduct locally and generate a propagated response.

An additional problem is the effect of the current strength of the drive stimulus S_1 on the ability of the premature stimulus to evoke a response. In the present study, the current intensity of S_1 always equaled that of S_2. There is evidence in isolated atrial tissue[4] that increasing the strength of S_1 will shorten the absolute refractory period of the tissue. Thus, current strength-effective refractoriness curves determined with constant current intensities of S_1 may be somewhat different from those of our study.

Furthermore, the spatial arrangement of the electrodes may have some influence on the current strength-effective refractoriness relation,[8] a factor not addressed in this study. In isolated tissue preparations, close bipolar plunge electrodes or microelectrodes are used to pass current and record. The interelectrode distances in these cases are much smaller than the 1 cm interelectrode distance found with the standard electrode catheters employed clinically. The effects of smaller interelectrode distances on the current strength-refractoriness relation in the human heart require further examination.

Clinical implications: Regardless of the cell mechanism, the current strength-effective refractory period relation does measure excitability of the ventricle as defined by how soon after a previous propagated response (S_1) and with how much current an extrastimulus (S_2) can elicit a propagated response. More importantly, the current strength-effective refractoriness relation can be used as a tool in clinical electrophysiology to assess accurately changes in ventricular excitability. Finally, the current strength-effective refractory period relation more precisely defines ventricular refractoriness, and may allow a more accurate analysis of reentrant arrhythmias and the effects of pacing or drugs on these arrhythmias.

Acknowledgment

We thank Marie Coscia and Bettie Kaplan for their assistance in preparing the manuscript. We also acknowledge the technicians in the Cardiac Electrophysiology Laboratory, and especially thank John A. Kastor, MD, Chief of the Cardiovascular Section, for his continued support and encouragement.

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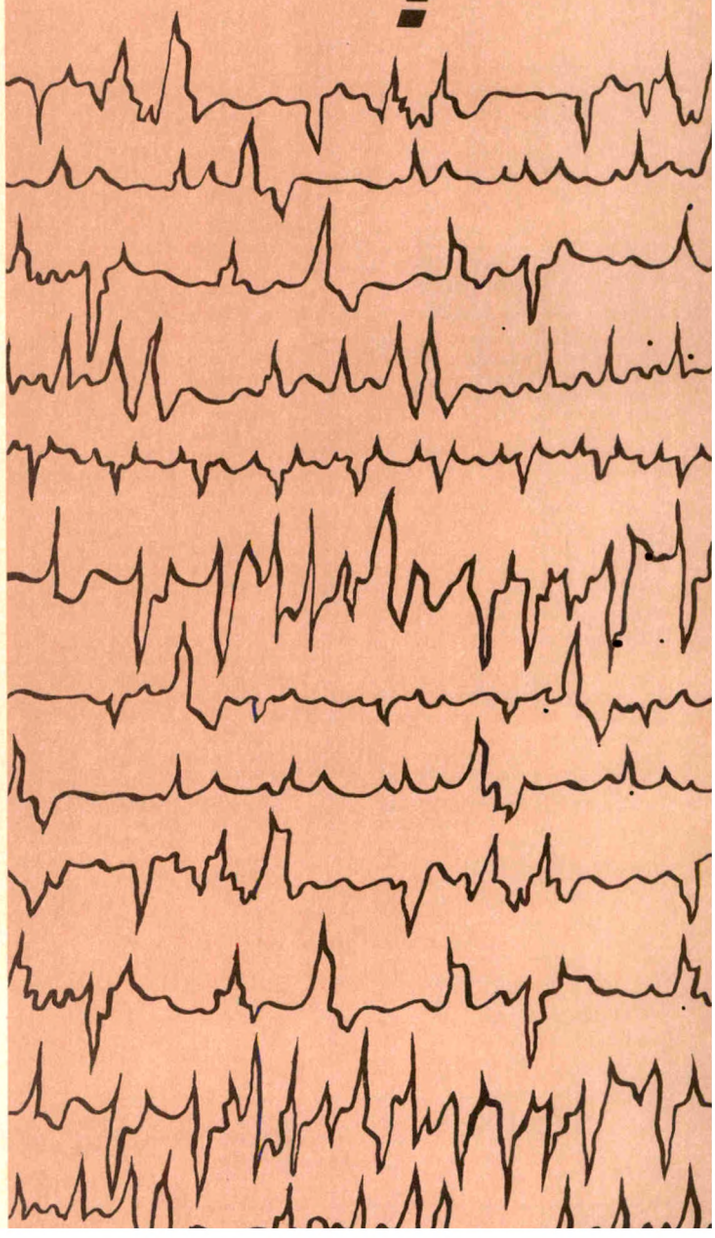

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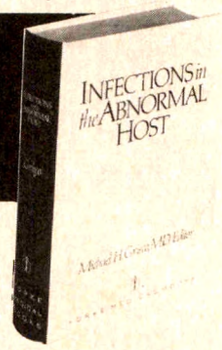

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Oral Norpace has not been adequately studied in patients with acute myocardial infarction or with persistent ventricular tachycardia or atrial arrhythmias and is not indicated for arrhythmias due to digitalis intoxication. The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.* ***Contraindications:*** *Cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.* ***Warnings: Norpace may cause or worsen congestive heart failure (CHF) or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily with primary cardiomyopathy or inadequately compensated CHF. Norpace should not be used in patients with uncompensated or marginally compensated CHF or hypotension unless the condition is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace, but careful attention must be given to maintaining cardiac function, including optimal digitalization. If hypotension occurs or CHF worsens, Norpace should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established. Norpace should be discontinued if significant widening (greater than 25%) of the QRS complex occurs. Prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If Q-T prolongation greater than 25% is observed and if ectopy continues, the patient should be monitored closely, and discontinuation of Norpace considered. In rare instances significant hypoglycemia has been reported during Norpace therapy. 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Because of its anticholinergic activity, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention, unless adequate overriding measures are taken.*** ***Precautions:*** *Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not allow a ventricular rate beyond physiologically acceptable limits. The effect of Norpace is presently uncertain in patients with sick sinus syndrome, Wolff-Parkinson-White syndrome, or bundle branch block. Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace. Norpace dosage should be reduced in patients with impaired renal or hepatic function and the electrocardiogram carefully monitored for signs of overdosage. Antiarrhythmic drugs may be ineffective in patients with hypokalemia. 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References: *1. Data on file, Searle Pharmaceuticals Inc. 2. Leahey, E.B., Jr., and others: The Effect of Quinidine and Other Oral Antiarrhythmic Drugs on Serum Digoxin: A Prospective Study, Ann. Intern. Med. 92:605-608 (May) 1980.*

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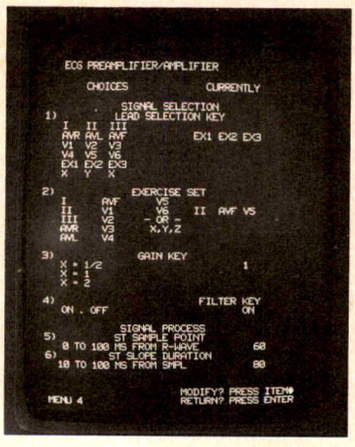

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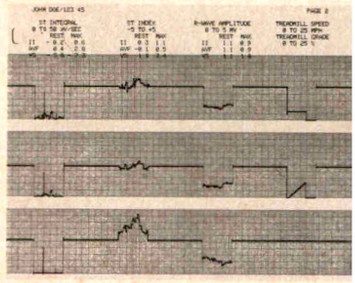

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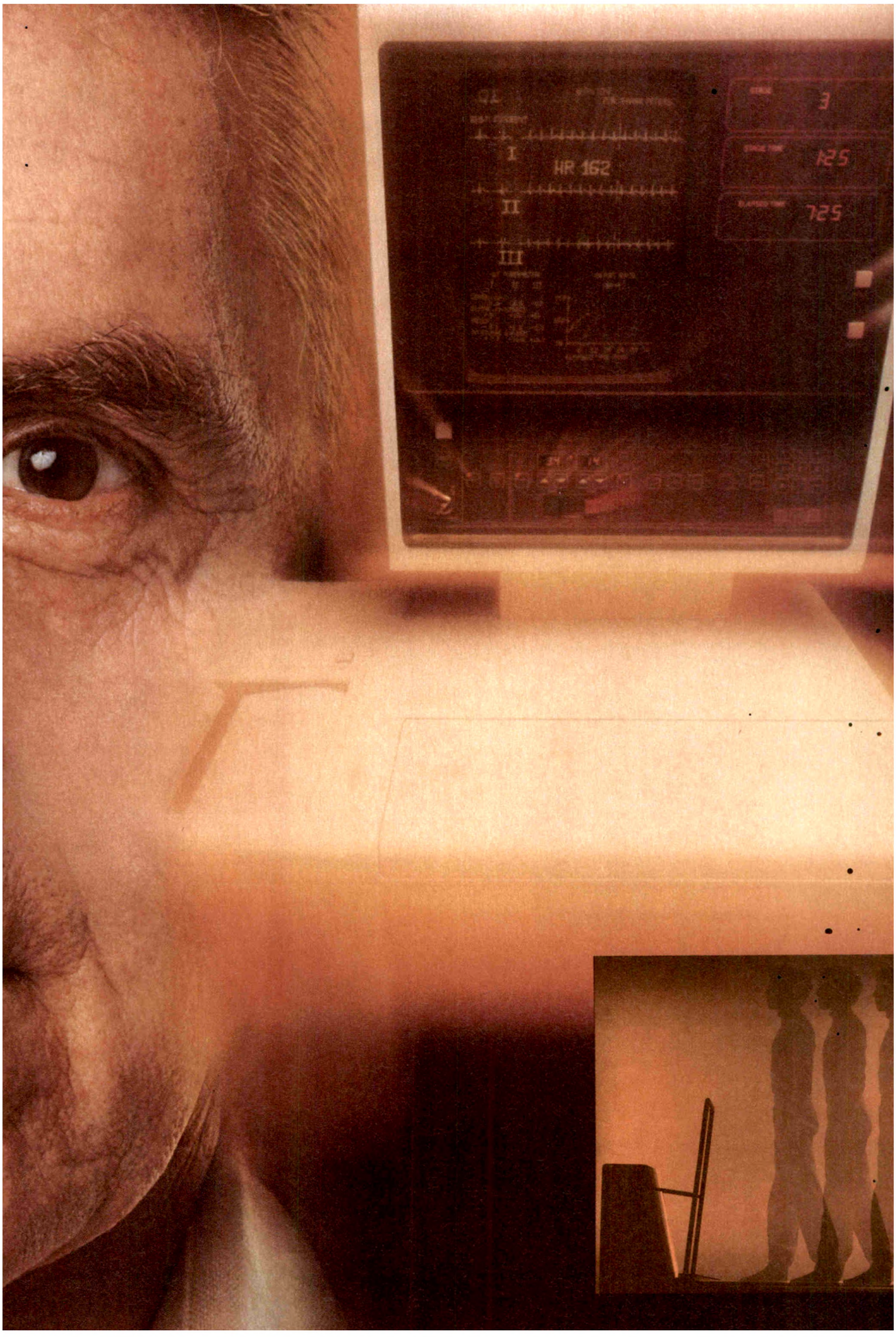
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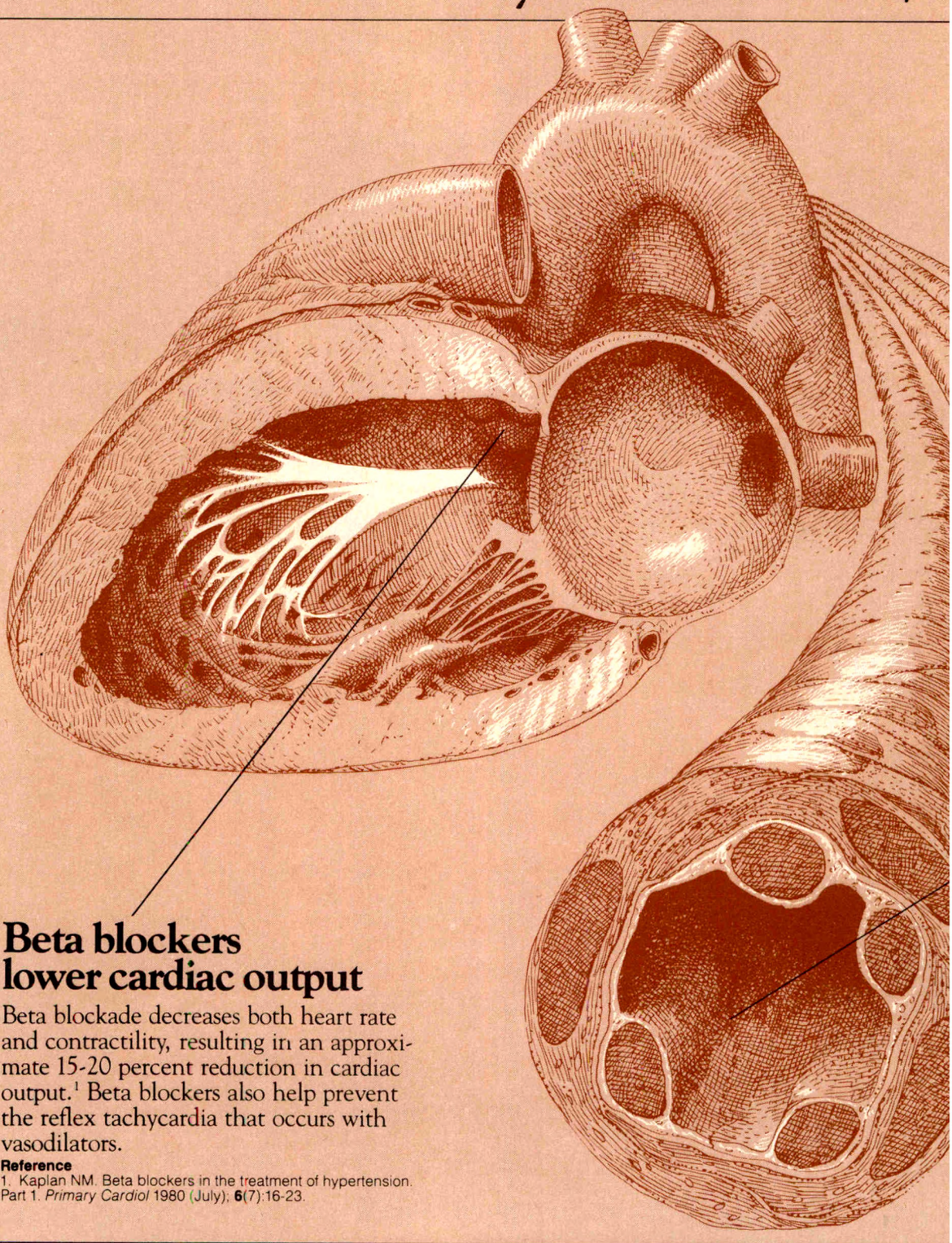

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Reference

1. Kaplan NM. Beta blockers in the treatment of hypertension. Part 1. *Primary Cardiol* 1980 (July); **6**(7):16-23.

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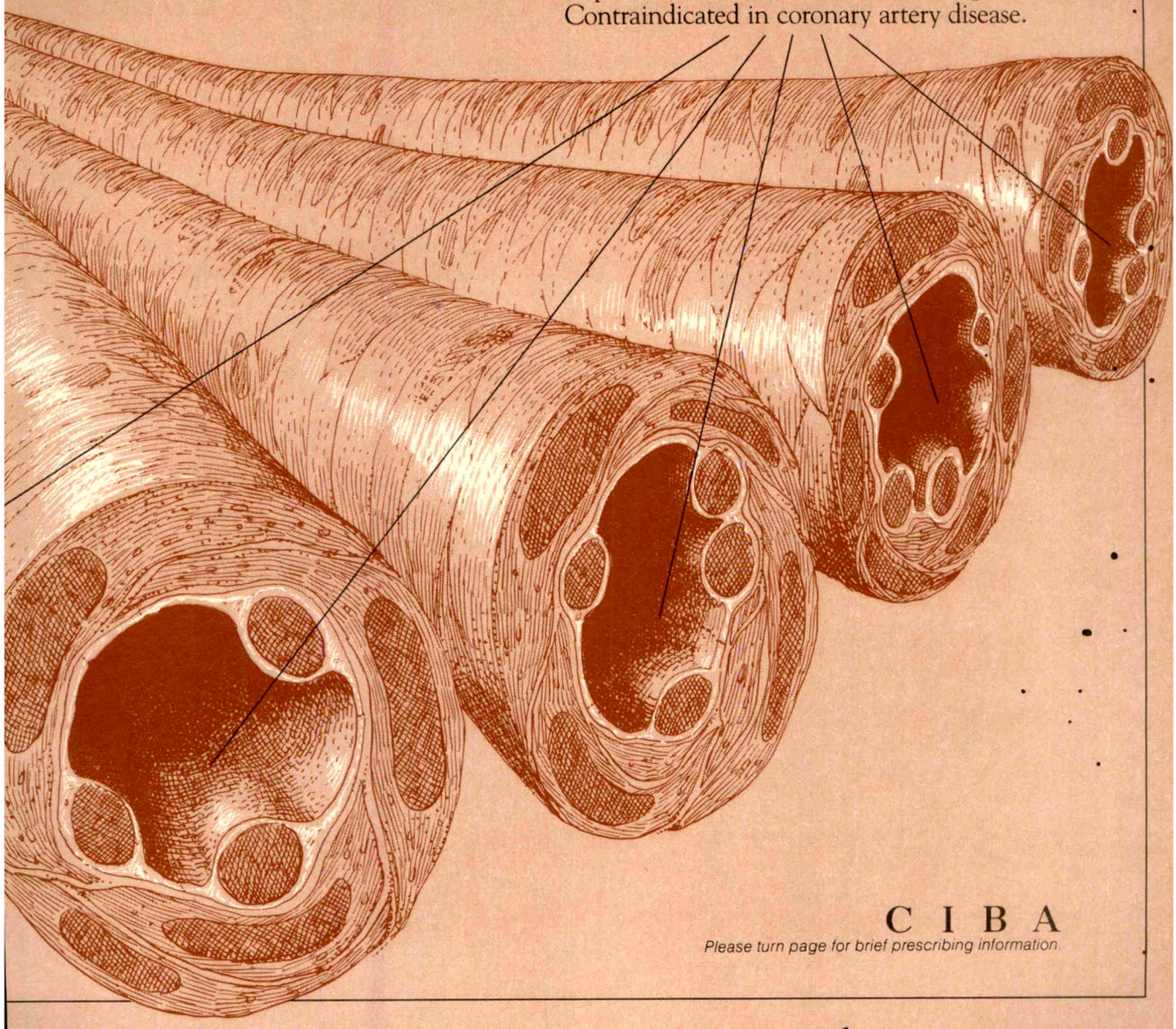

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WARNINGS
Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary. Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms. A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.
Use MAO inhibitors with caution in patients receiving hydralazine.
When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure.
Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.
Usage in Pregnancy
Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.
PRECAUTIONS
Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease. The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine. Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.
In hypertensive patients with normal kidneys who are treated with Apresoline, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improved renal function has been noted where control values were below normal prior to Apresoline administration. However, as with any antihypertensive agent, Apresoline should be used with caution in patients with advanced renal damage.
Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop. Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.
The Apresoline tablets (10 and 100 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.
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Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.
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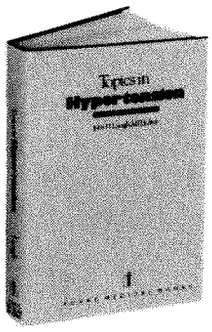

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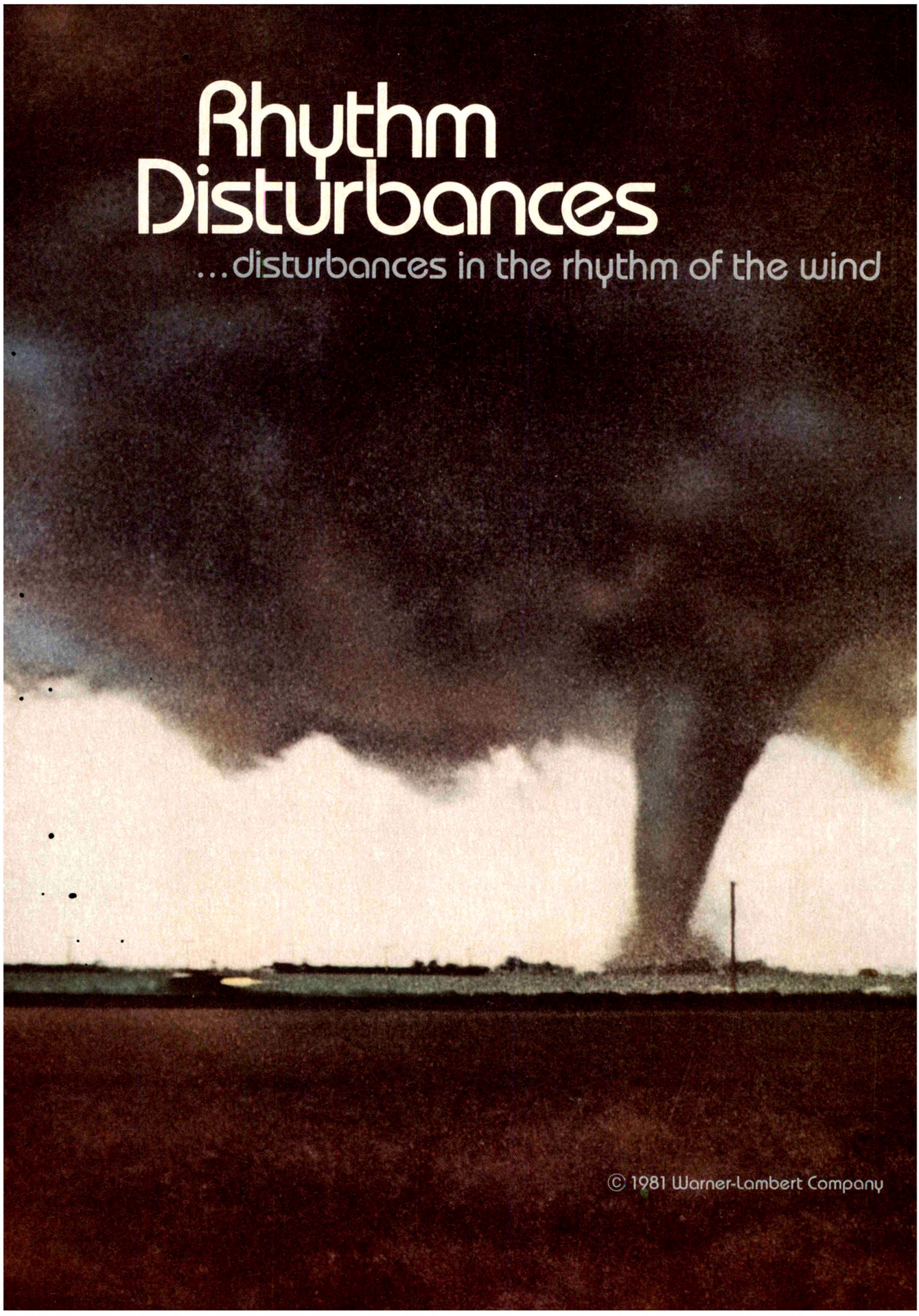
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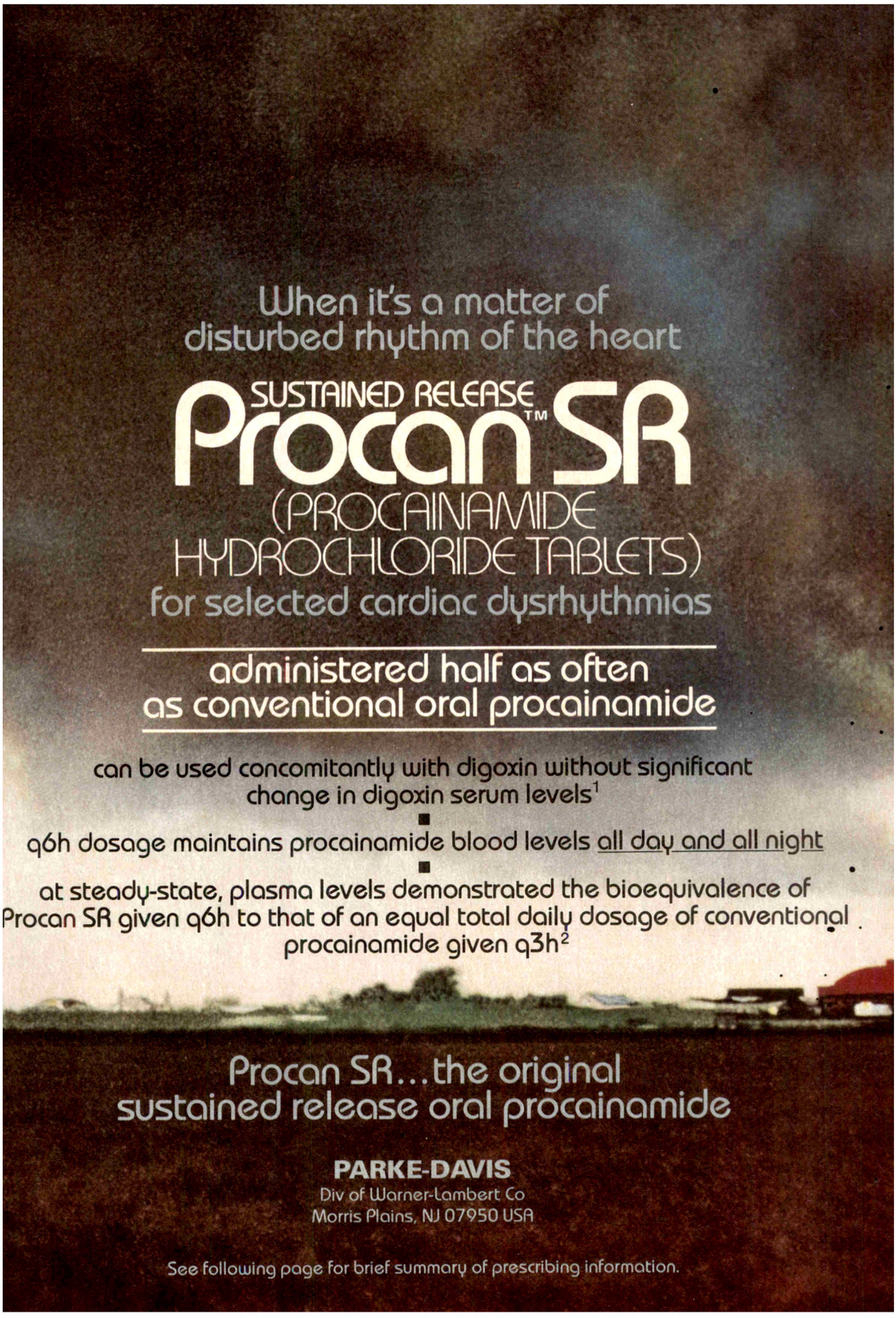
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The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient re-evaluated because asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney diseases, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome. Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patient receiving maintenance procainamide therapy.

ADVERSE REACTIONS: Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS). Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride tablets) are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dosage of 50 mg/kg of body weight given at three-hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

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Atrial fibrillation and paroxysmal atrial tachycardia—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dosage of 0.5 g to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

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2. Smith TC, Kinkel AW: Plasma levels of procainamide after administration of conventional and sustained-release preparations. *Curr Therap Res* 27: 217- 228, 1980.

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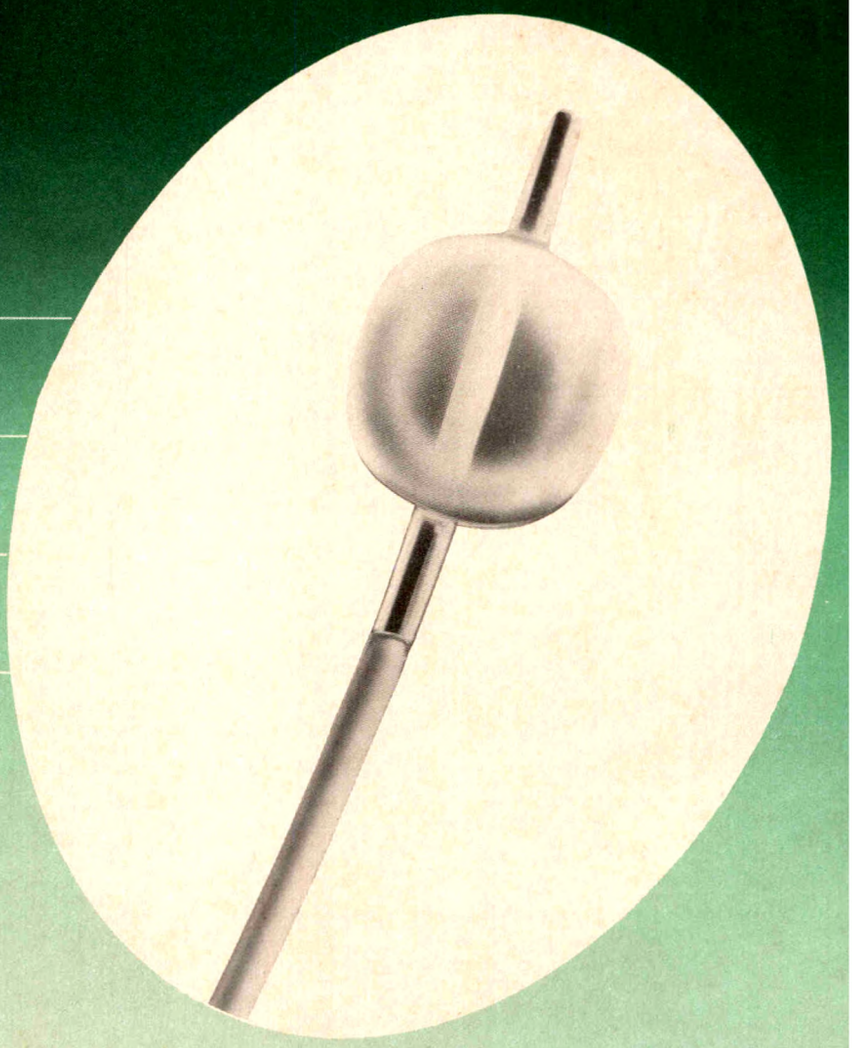

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Extra-Adrenergic Mechanisms Responsible for the Effects of Glucose-Insulin-Potassium Solution on Vulnerability to Ventricular Fibrillation

WESLEY W. BROOKS, DSc*
RICHARD L. VERRIER, PhD, FACC
BERNARD LOWN, MD, FACC

Boston, Massachusetts

In 53 chloralose-anesthetized dogs, the actions of glucose (10 mg/kg per min), insulin (0.025 U/kg per min) and potassium (0.025 mEq/kg per min) on the ventricular fibrillation and repetitive extrasystole thresholds were examined. Measurements were initially made in the control state and then repeated at 30, 60 and 120 minutes of infusion of glucose-insulin-potassium solution at a constant rate of 1.23 ml/min. The dogs received on the average 36 g of glucose, 44 U of insulin and 44 mEq of potassium over a 2 hour period. In the nonischemic myocardium, the infusion raised the threshold for ventricular fibrillation and repetitive extrasystole to a peak of 94 and 61 percent, respectively, without significantly changing serum potassium or circulating catecholamine concentration. In the ischemic myocardium, the incidence of spontaneous ventricular fibrillation during 10 minutes of coronary occlusion was reduced from 83 percent in the control state to 17 percent with glucose-insulin-potassium infusion. However, the infusion did not alter the incidence of ventricular fibrillation associated with reperfusion.

Because cardio-cardiac sympathetic reflexes are elicited in response to coronary occlusion, the effect of glucose-insulin-potassium infusion on ventricular vulnerability during left stellate ganglion stimulation and norepinephrine infusion was investigated. The infusion completely prevented the reduction in the vulnerable period threshold during stellate stimulation and norepinephrine infusion. Furthermore, the peak protection afforded by the infusion was greater than that achieved with beta adrenergic blockade and was still present in catecholamine-depleted hearts.

It is concluded that infusion of glucose-insulin-potassium solution protects against ventricular fibrillation in the normal and ischemic canine heart but not during reperfusion. This protection may be due in part to antagonism of adrenergic activity; however, the primary influence of the solution is mediated by extra-adrenergic mechanism.

From the Cardiovascular Research Laboratories, Department of Nutrition, Harvard School of Public Health, and Department of Medicine, Harvard Medical School, Boston, Massachusetts. This study was supported in part by Grant MH-2184 from the National Institute of Mental Health and Grant HL-07776 from the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Public Health Service, Bethesda, Maryland. Manuscript received June 9, 1980; revised manuscript received July 26, 1980, accepted September 9, 1980.

* This work was performed during tenure of a Vittorio deNora/Diamond Schamrock Corporation fellowship.

Address for reprints: Bernard Lown, MD, Cardiovascular Research Laboratories, Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, Massachusetts 02115.

In 1957, Cherbakoff et al.[1] showed that infusion of insulin and glucose prevented ventricular arrhythmias and fibrillation in experimental animals subjected to myocardial infarction. This finding was confirmed by Sodi-Pallares et al.,[2] who demonstrated diminished excitability of the ischemic myocardium after treatment with glucose-insulin-potassium solution. This therapy has received widespread clinical application for the prevention of ventricular arrhythmias after acute myocardial infarction.[2–6] However, the mechanism by which the solution affects cardiac electrical properties remains poorly defined. The protective effect of the solution has been ascribed to reduced potassium efflux from ischemic myocardial cells.[1,7] But insulin has been shown to protect the normal canine heart against ventricular fibrillation when shifts in extracellular potassium were prevented.[8] Hiatt et al.,[9] using pharmacologic doses of insulin, demonstrated a protective effect against ventricular

arrhythmias in dogs subjected to ligating the left circumflex coronary artery. They attributed this beneficial result to insulin blocking the action of catecholamines.[10]

The present study was undertaken to determine whether the action of glucose-insulin-potassium solution protects against fibrillation ensuing from coronary arterial occlusion as well as from reperfusion. There is evidence indicating that the former but not the latter is neurally mediated.[11,12] A further objective was to define the interaction between sympathetic neural activity and glucose-insulin-potassium solution as related to the salutary action of this solution on ventricular vulnerability to fibrillation.

Methods

Experimental preparation: Fifty-three healthy mongrel dogs of either sex, weighing 10 to 20 kg, were utilized. They were anesthetized with intravenous alpha chloralose (100 mg/kg, Sigma Chemical 10 percent weight in volume) and additional increments of 50 mg/kg were given when required to maintain a constant level of anesthesia. The animals were ventilated with a mixture of room air and 100 percent oxygen through a cuffed endotracheal tube using a Harvard respirator resulting in a concentration of 40 percent oxygen. Arterial oxygen tension was kept between 100 and 125 mm Hg and arterial pH between 7.35 and 7.45. A polyethylene catheter inserted into a femoral artery was used for sampling arterial blood and for monitoring blood pressure by means of a Statham P23Db transducer.

Cardiac Testing

Electrical testing of the heart was begun 30 minutes after induction of anesthesia and was accomplished by means of an intracavitary lead system consisting of a transvenous bipolar pacing catheter (Medtronic 5819 platinum electrodes with an interelectrode distance of 1.5 cm [width 3 mm] and electrocardiographic recording probe (USCI® semi-floating probe 003992-4F). The recording catheter terminated 20 mm proximally to the pacing catheter. The catheter system was positioned under fluoroscopic control at the apex of the right ventricle by way of a jugular vein. A Medtronic pacemaker was employed to deliver rectangular pulses of 2 ms duration at intervals of 300 ms. This rate (200 beats/min) was maintained constant during all determinations. The pacemaker current was adjusted to twice the mid diastolic threshold. The distal pole of the pacemaker catheter was made cathodal. Testing impulses of 5 ms duration were generated using a constant current Grass S44 square wave pulse generator (±1 percent current and its time accuracy) with an electrically isolated output and delivered through the bipolar pacing catheter. The pulse generator was equipped with appropriate circuitry to inhibit the output of the pacemaker for 1.5 seconds after delivery of the test stimulus, which occurred after every 12 to 15 paced beats.

Determination of the repetitive extrasystole and ventricular fibrillation thresholds: Measurement of the vulnerable period threshold was performed as follows: Electrical diastole was scanned by means of a test stimulus of 5 ms duration and an initial current of 8 mA. The scanning was conducted at 5 ms increments, beginning at the border of the absolute refractory period and ending at the apex of the T wave.[13,14] If no repetitive extrasystoles were induced, the stimulus intensity was increased in 2 mA steps and scanning was continued until repetitive extrasystoles were elicited. The lowest stimulus intensity that evoked repetitive ventricular responses in two of three trials defined the repetitive extrasystole threshold. Thereafter, the vulnerable period was scanned to define the ventricular fibrillation threshold. These determinations were made before and after each experimental intervention.

Defibrillation was accomplished, usually within 3 to 5 seconds, with a direct current pulse (100 to 200 watt-s capacitor discharge from a Lown cardioverter) delivered through a pair of copper plates (150 cm^2) previously fastened across the thorax.

Experimental Interventions

Glucose-insulin-potassium infusions: The dogs received 148 ml of a solution of glucose, insulin and potassium administered intravenously for 2 hours at a rate of 10 mg/kg body weight per min for glucose, 0.025 U/kg per min for insulin and 0.025 mEq/kg per min for potassium. Thus, a total of 36 g of glucose, 44 U of insulin and 44 mEq of potassium was administered to the treated animals, which weighed an average of 15 kg. Electrical testing was performed in the control state as well as at 30 minutes and 1 and 2 hours after the onset of the infusions. Serum potassium and glucose concentrations were determined at the time of electrical testing. In addition, circulating catecholamines were measured in response to glucose-insulin-potassium infusion according to a single isotope radioenzyme assay.[15]

Influence of glucose-insulin-potassium infusion on incidence of ventricular fibrillation during myocardial ischemia and reperfusion: The dogs were anesthetized with alpha-chloralose and fitted with instruments as described. A thoracotomy was performed through the fourth left intercostal space and the heart exposed after a pericardiectomy. The origins of the left anterior descending and circumflex coronary arteries were dissected. A snare of 2-0 silk suture was placed around either artery as close to its origin as possible.

The incidence of ventricular fibrillation after a 10 minute period of occlusion and subsequent reperfusion of either the left anterior descending or left circumflex coronary artery was recorded. The heart rate was maintained constant at 200 beats/min by ventricular pacing. The dogs were randomly assigned to either a control group or a glucose-insulin-potassium pretreatment group. In the latter group, infusion was begun 60 minutes before coronary occlusion and was terminated 2 minutes after reperfusion.

Effect of glucose-insulin-potassium on vulnerability induced by adrenergic stimulation: stellate ganglion stimulation: Stellate stimulation was accomplished with stimuli of 5 to 15 V, 5 ms duration and 10 hertz delivered to the main body of the decentralized ganglion. In these experiments, the cervical vagi were sectioned bilaterally and the contralateral stellate ganglion was removed. Thus, the direct effects of unilateral stimulation could be observed without activating the contralateral ganglion. A 15 minute rest period was allowed before cardiac electrical testing was begun. The effects of stellate ganglion stimulation on the repetitive extrasystole and ventricular fibrillation thresholds were studied with and without infusion of glucose-insulin-potassium solution beginning 60 minutes before stellate ganglion stimulation.

Pharmacologic Interventions

Norepinephrine infusion: Norepinephrine bitartrate (Levophed®, Winthrop) in normal saline solution was infused intravenously at a rate of 0.5 μg (base)/kg per min. This agent was administered for a period of 15 minutes before the effect of norepinephrine on the repetitive extrasystole and ven-

tricular fibrillation thresholds was tested. This dose of norepinephrine increases vulnerability to fibrillation without significantly altering mean arterial blood pressure. The threshold values during norepinephrine infusion were determined at 15 and 30 minutes after the start of infusion.

In a second group of dogs, glucose-insulin-potassium was administered intravenously at a rate of 10.00 mg/kg per min for glucose, 0.025 U/kg per min for insulin and 0.025 mEq/kg per min for potassium. Norepinephrine was added to this stock solution at a concentration that resulted in an infusion rate of 0.5 μg (base)/kg per min. The effects of concurrent administration of norepinephrine and glucose-insulin-potassium were examined 15 and 30 minutes after infusion.

Beta adrenergic blockade: Six dogs were subjected to beta adrenoceptor blockade using a single intravenous dose of propranolol (0.25 mg/kg Inderal®, Ayerst). This dose produces a high degree of blockade without altering myocardial membrane stability.[16]

Catecholamine depletion: Depletion of myocardial catecholamine stores was accomplished in 5 dogs by an intramuscular injection of 0.3 mg/kg of reserpine on 2 consecutive days before definitive study. This dose of reserpine reduces tissue stores of norepinephrine to chemically undetectable levels.[17]

Statistical analysis: The results were analyzed using Student's *t* test for paired and unpaired data. The criterion of significance was a probability (p) level of <0.05.

Results

Effect of glucose-insulin-potassium infusion in normal dogs: Administration of glucose, insulin and potassium resulted in an increase in fibrillation threshold in six dogs from a mean control value (± standard error of the mean) of 31 ± 4 to 48 ± 6 mA after 30 minutes ($p < 0.01$), 48 ± 3 mA after 1 hour and 60 ± 8 mA after 2 hours of infusion (Fig. 1). The threshold for inducing repetitive ventricular responses likewise increased from 23 ± 3 to 31 ± 5 mA after 30 minutes ($p < 0.05$), 33 ± 3 mA after 1 hour and 37 ± 3 mA after 2 hours of infusion. Plasma potassium concentration was not significantly altered but did tend to rise from control levels of 2.95 ± 0.21 to 3.25 ± 0.21 mEq/liter. The plasma glucose level increased from 89 ± 4 to 209 ± 22 mg/100 ml at the end of 2 hours of glucose-insulin-potassium infusion ($p < 0.001$). No correlation was evident between the magnitude of changes in plasma glucose concentration and the extent of change in the repetitive extrasystole and ventricular fibrillation thresholds.

Infusion of glucose-insulin-potassium resulted in a significant decrease in intrinsic heart rate from a control value of 148 ± 12 to 122 ± 10 beats/min after 1 hour and 118 ± 7 beats/min after 2 hours ($p < 0.01$) (Fig. 1). Mean arterial blood pressure did not significantly change. Serum concentrations of circulating catecholamines tended to decrease with glucose-insulin-potassium infusion, but were not significantly lower than control levels at the end of 2 hours (epinephrine 63 ± 30 to 29 ± 10 pg/ml and norepinephrine 216 ± 35 to 204 ± 29 pg/ml).

Effect of glucose-insulin-potassium on vulnerability during myocardial ischemia and reperfusion: Glucose-insulin-potassium infusion-induced protection against ventricular fibrillation was studied

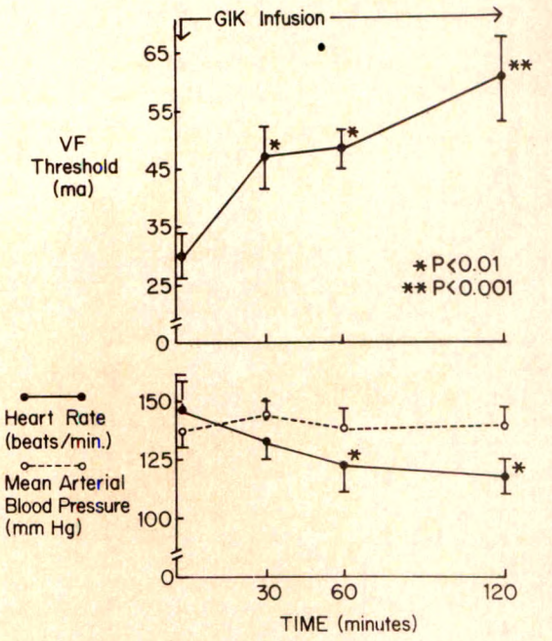

FIGURE 1. Effect of glucose-insulin-potassium (GIK) infusion on heart rate, arterial blood pressure and ventricular fibrillation (VF) threshold in six normal dogs. The infusion produced a moderate decrease in heart rate, did not alter mean arterial blood pressure and resulted in a significant increase in ventricular fibrillation threshold. P = probability.

in 24 dogs after 10 minutes of occlusion of either the left anterior descending or left circumflex coronary artery. In a group of 6 dogs, glucose-insulin-potassium infusion was begun 60 minutes before occlusion of the circumflex coronary artery. During control occlusion, five (83 percent) of six dogs manifested ventricular fibrillation, whereas after glucose-insulin-potassium infusion, only 1 of 6 dogs demonstrated this arrhythmia ($p < 0.01$). However, pretreatment with glucose-insulin-potassium did not decrease the incidence of ventricular fibrillation during release-reperfusion in animals subjected to left anterior descending coronary arterial occlusion (Fig. 2).

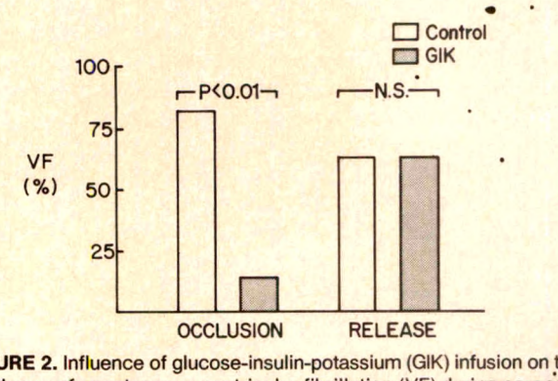

FIGURE 2. Influence of glucose-insulin-potassium (GIK) infusion on the incidence of spontaneous ventricular fibrillation (VF) during coronary arterial occlusion and release. The infusion provided significant protection against ventricular fibrillation during occlusion of the left circumflex coronary artery, but did not protect with release of occlusion of the left anterior descending coronary artery. N.S. = not significant.

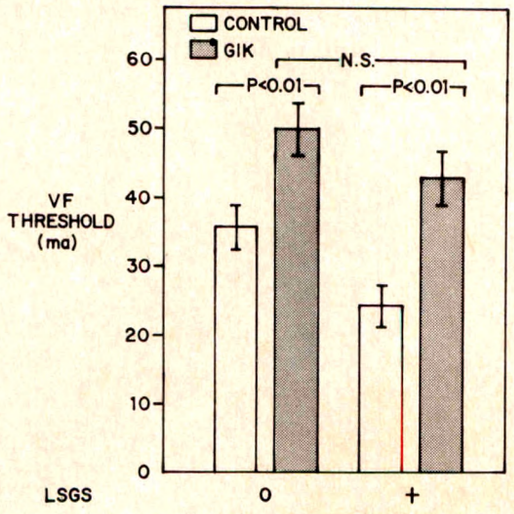

FIGURE 3. Effect of glucose-insulin-potassium (GIK) infusion on ventricular fibrillation (VF) threshold during sympathetic neural stimulation. In vagotomized dogs with stellate ganglia decentralized, left stellate ganglion stimulation (LSGS) (+) decreased the ventricular fibrillation threshold from 36 to 24 mA (33 percent [$p < 0.01$]). Glucose-insulin-potassium infusion during concurrent stellate ganglion excitation (+) prevented this change in ventricular fibrillation threshold.

Influence of glucose-insulin-potassium on vulnerability induced by adrenergic stimulation: Left stellate ganglion stimulation in six dogs resulted in a significant reduction in both the repetitive extrasystole threshold (from 21 ± 2 to 14 ± 2 mA, $p < 0.05$) and the ventricular fibrillation threshold (from 36 ± 2 to 24 ± 4 mA, $p < 0.01$). Glucose-insulin-potassium infusion for 60 minutes raised the baseline ventricular fibrillation threshold (from 36 ± 2 to 52 ± 6 mA, $p < 0.05$) and the repetitive extrasystole threshold (from 21 ± 2 to 28 ± 2 mA, $p < 0.05$). Moreover, the infusion, prevented the decrease in the ventricular fibrillation threshold and repetitive extrasystole threshold (from 28 ± 2 to 23 ± 4 mA, difference not significant) produced by sympathetic neural activation (Fig. 3).

The effect of norepinephrine infusion on the vulnerable period threshold was also substantially altered by administration of glucose-insulin-potassium infusion. Norepinephrine infusion in six dogs lowered both the repetitive extrasystole threshold (from 18 ± 2 to 11 ± 2 mA, $p < 0.05$) and the ventricular fibrillation threshold (from 28 ± 4 to 18 ± 2 mA, $p < 0.01$). Concurrent infusion of glucose-insulin-potassium solution for 30 minutes abolished the norepinephrine-induced reduction in the vulnerable period threshold (Fig. 4).

Beta adrenergic blockade: In six dogs, propranolol (0.25 mg/kg) resulted in a 29 percent increase in both the repetitive extrasystole threshold (from 21 ± 2 to 27 ± 3 mA, $p < 0.05$) and the ventricular fibrillation threshold (from 31 ± 3 to 40 ± 2 mA, $p < 0.01$). The magnitude of protection afforded by beta adrenergic blockade was significantly less than that provided by glucose-insulin-potassium infusion (Fig. 5). After administration of glucose-insulin-potassium to an additional group of six dogs, the repetitive extrasystole threshold increased by 61 percent ($p < 0.05$) and the ventricular fibrillation threshold by 94 percent at peak effect.

Effect of glucose-insulin-potassium on ventricular fibrillation threshold in dogs pretreated with reserpine: In five dogs, pretreatment with reserpine (0.3 mg/kg) resulted in a repetitive extrasystole threshold of 26 ± 3 mA and a ventricular fibrillation threshold of 48 ± 6 mA. In these dogs, glucose-insulin-potassium administration increased the ventricular fibrillation threshold from 48 ± 6 to 74 ± 12 mA after 30 minutes ($p < 0.01$) and to 77 ± 13 mA after 1 hour and 72 ± 11 mA after 2 hours of infusion (Fig. 6). The threshold for inducing repetitive ventricular responses increased from 26 ± 3 to 33 ± 6 mA after 30 minutes ($p < 0.05$) and to 38 ± 2 mA after 1 hour and 42 ± 6 mA after 2 hours of glucose-insulin-potassium infusion.

Discussion

These results confirm previous observations demonstrating the potent effect of glucose-insulin-potassium infusion in raising the threshold for ventricular fibrillation in both the normal as well as the acutely ischemic heart. However, pretreatment with these agents did not protect the heart during reperfusion after a 10 minute period of coronary arterial occlusion. Glucose-insulin-potassium infusion prevented the decrease in the vulnerable period threshold produced by sympathetic neural or humoral stimulation. The salutary effect was more pronounced than that achieved by beta adrenoceptor blockade and was not annulled by depletion of cardiac catecholamines.

Mechanism of diminished susceptibility to ventricular fibrillation: The electrophysiologic mechanism whereby glucose-insulin-potassium solution diminishes cardiac susceptibility to ventricular fibrillation during acute coronary occlusion is undefined. The fact that the solution raises the fibrillation threshold in the normal dog as well as lessening the incidence of spon-

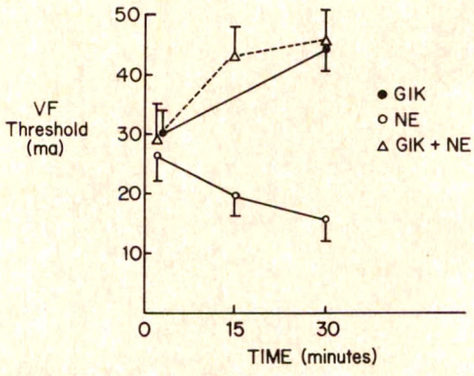

FIGURE 4. Effect of glucose-insulin-potassium (GIK) infusion on ventricular fibrillation (VF) threshold during sympathetic humoral stimulation. Norepinephrine (NE) infusion (0.5 μg/kg per min) for 30 minutes in neurally intact animals decreased the ventricular fibrillation threshold by 36 percent ($p < 0.01$). Glucose-insulin-potassium infusion during concurrent norepinephrine infusion increased the ventricular fibrillation threshold 53 percent above control value, to levels observed with glucose-insulin-potassium infusion alone.

taneous ventricular fibrillation after coronary occlusion suggests that the protection afforded may not depend on the presence of myocardial ischemia. The disparity of action of the solution on the malperfused and reperfused heart further emphasizes that disparate electrophysiologic mechanisms are implicated in these two conditions. Several diverse actions of the polarizing solution may account for the antifibrillatory effect noted during coronary occlusion. In the ischemic canine model, glucose-insulin-potassium administration reduces myocardial damage. This is indicated by the lessened S-T segment changes, decreased depletion of myocardial creatine kinase and glycogen, diminished electron microscopic changes,[18,19] improvement in hemodynamic function[20] and a decrease in ventricular arrhythmias.[1,7,21] Cherbakoff et al.[1] found that infusion of 400 ml of 50 percent dextrose in water plus 70 to 200 U of regular insulin for 2 hours prevented ventricular arrhythmias and delayed the onset of ventricular fibrillation in dogs subjected to acute ligation of the left circumflex coronary artery. However, ventricular vulnerability during reperfusion was not examined. The protective effect of glucose-insulin-potassium solution was ascribed to reduced potassium efflux from ischemic myocardial cells. Recently Obeid et al.[8] demonstrated a protective effect of glucose, insulin and potassium on vulnerability to ventricular fibrillation in the nonischemic dog myocardium. The heart was protected even when extracellular potassium was maintained at a low concentration by hemodialysis.

Role of reduced myocardial free fatty acid uptake: Glucose-insulin-potassium infusion has been shown to decrease circulating free fatty acid concentrations in both animals[22] and human beings.[6] The resultant decrease in myocardial free fatty acid uptake in response to the infusion has been postulated to be a basis for the therapeutic action on the ischemic heart.[2] Indeed, a recent report by Rogers et al.[6] demonstrated a reduction in premature ventricular complexes and ventricular tachycardia in acute myocardial infarction in patients treated with glucose-insulin-potassium infusion as compared with control subjects. Free fatty acid levels were significantly lowered in recipients of the infusion and were substantially lower in patients having a paucity of premature ventricular complexes.[6] Although free fatty acid concentration was not measured in our study, we can assume that, because similar concentrations of glucose, insulin and potassium were employed, the level of free fatty acids decreased. Thus a reduction in free fatty acid concentration should be considered a possible mechanism for the salutary action of glucose-insulin-potassium solution on vulnerability of the heart to fibrillation. Nevertheless, Ahmed et al.[2] found the beneficial effect of the solution on myocardial function to be unrelated to a reduction in the level of free fatty acids.

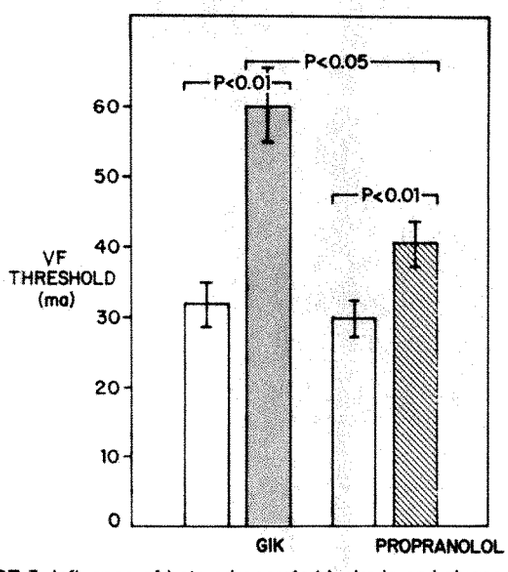

FIGURE 5. Influence of beta adrenergic blockade and glucose-insulin-potassium (GIK) infusion on the ventricular fibrillation (VF) threshold. Propranolol (0.25 mg/kg) administered in an intravenous bolus dose to six neurally intact dogs significantly raised the ventricular fibrillation threshold by 29 percent, whereas in another group of six dogs glucose-insulin-potassium infusion for 2 hours raised the threshold by 94 percent.

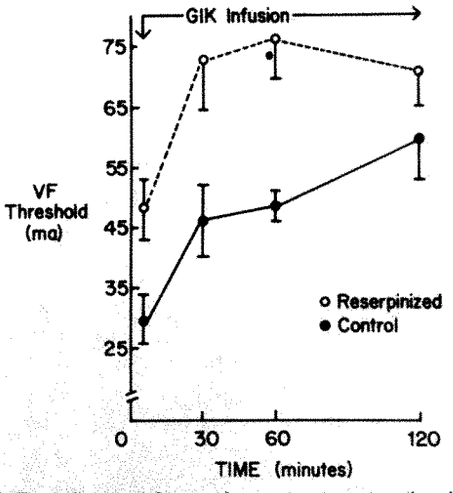

FIGURE 6. The influence of reserpine pretreatment on the changes in ventricular fibrillation (VF) threshold induced by glucose-insulin-potassium (GIK) infusion. In five dogs pretreated with reserpine (0.3 mg/kg), glucose-insulin-potassium administration further raised the ventricular fibrillation threshold.

Role of reduced profibrillatory effect of sympathetic neural and neurohumoral activities: Hiatt et al.[9] demonstrated that large doses of insulin and 10 percent dextrose in water had a protective effect against ventricular arrhythmias in dogs subject to circumflex coronary arterial ligation. They conjectured that the response was the consequence of insulin blocking the action of catecholamines. Such a mechanism was suggested from observations in nonischemic dogs in which insulin prevented arrhythmias induced by epinephrine and isoproterenol.[10] Our data demonstrate that glucose-insulin-potassium infusion indeed prevents the reduction in ventricular fibrillation threshold after norepinephrine administration or stellate ganglion stimulation. The similarity of results obtained with different experimental approaches for augmenting

adrenergic activity supports the hypothesis that the glucose-insulin-potassium solution antagonized the profibrillatory effect of sympathetic neural and neurohumoral activity. This view would also account for the protection the solution affords the ischemic myocardium because potent cardio-cardiac sympathetic reflexes are promptly elicited in response to coronary occlusion.[11,12] Our finding that glucose-insulin-potassium infusion also raised the ventricular fibrillation threshold in dogs treated with reserpine indicates that such a mechanism cannot fully account for the protective actions of the infusion. Furthermore, the magnitude of protection with the infusion was considerably greater than that resulting from beta adrenergic blockade. Rossi et al.[24] reported that glucose, insulin and potassium solution administered to patients was antiarrhythmic even after beta adrenergic blockade.

Direct electrophysiologic effects: In the study of Obeid et al.,[8] it was noted that glucose-insulin-potassium infusion prevented degeneration to ventricular fibrillation or, once ventricular fibrillation was present, caused spontaneous resumption of sinus rhythm. These animals were normal and without myocardial ischemia. Although the underlying mechanism was not elucidated, a direct electrophysiologic action of glucose-insulin-potassium solution on the heart seems plausible. Several studies have suggested that a "membrane" effect might be the major factor accounting for the action of the solution.[22,25,26]

Glucose administration promotes potassium uptake into the cell[21] and reduces potassium loss from ischemic myocardium,[27] resulting in hyperpolarization and improved local conduction velocity. This theoretically should reduce the incidence of so-called slow response potentials.[28] Insulin further enhances glucose uptake, resulting in greater hyperpolarization and further stabilizing the membrane potential.[29] Thus, these electrophysiologic responses to glucose-insulin-potassium solution could account for the enhanced electrical stability observed in ischemic as well as in nonischemic myocardium.

Lack of effect with coronary reperfusion: In contrast to its effects on vulnerability during occlusion, glucose-insulin-potassium administration did not alter the incidence of fibrillation with reperfusion. The mechanism whereby ventricular fibrillation is precipitated during reperfusion of ischemic myocardium remains uncertain. However, there is evidence that washout products of cell ischemia may be involved.[30] It has been demonstrated that if blood flow is gradually restored to the ischemic myocardium[31,32] or if perfusion is maintained with deoxygenated fluid, the incidence of ventricular arrhythmias on reinstitution of flow is reduced.[31–34] The finding that ventricular fibrillation ensues within seconds after reinstitution of coronary arterial flow also argues for washout of metabolic products.[30] Recently, Downar et al.[35] showed that "ischemic" blood obtained from local coronary veins during release of coronary occlusion in pigs exerts a potent depressant effect on excitability of even normal myocardium.

Thus, there is evidence that the release of blood constituents provide a potent stimuli for triggering ventricular fibrillation. Beta adrenergic blockade[36,37] or cardiac membrane stabilization with lidocaine[36] has proved ineffectual in preventing vulnerability during release. Because the influence of glucose-insulin-potassium solution on vulnerability derives from its antiadrenergic and membrane stabilizing effects, it is therefore not unanticipated that it did not protect during release-reperfusion.

Clinical considerations: The present findings are consistent with recently accumulating clinical evidence[6] indicating a substantial antiarrhythmic action of glucose-insulin-potassium solution. The protective effect appears to be partly due to the solution's antiadrenergic influence and partly to its cardiac membrane-stabilizing action. Because insulin is the primary component that alters ventricular vulnerability,[8] it is possible that changes in endogenous insulin levels may also influence ventricular electrical properties. This supposition is supported by our preliminary studies showing that intravenous administration of glucose in a dose comparable with that used in a standard glucose tolerance test significantly increases the vulnerable period threshold. The effects of glucose administration on vulnerability correlate with the changes in insulin blood levels and are completely prevented by blocking endogenous insulin secretion with diazoxide. The possibility that spontaneous fluctuations in insulin blood levels in response to physiologic and pathophysiologic states can influence vulnerability deserves further exploration.

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Lack of Effect of Aspirin on Myocardial Infarct Size in the Dog

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Pretreatment with platelet-inhibitory doses of aspirin (3 mg/kg body weight) has been shown to augment epicardial collateral flow by more than 50 percent ($p < 0.05$) 4 hours after ligation of the left anterior descending coronary artery in dogs. To determine whether this favorable influence of aspirin is sufficient to decrease the amount of infarcted tissue, either intravenous aspirin, 3 mg/kg ($n = 17$), or saline solution ($n = 17$) was administered to dogs 10 minutes before occlusion of the left anterior descending coronary artery. Administration of saline solution or aspirin was repeated every 24 hours. By 72 hours, 5 dogs in each treatment group had died. Survivors were killed at 72 hours. The portion of the left ventricle at risk of infarction was delineated by perfusion of the aortic root with Evans blue and simultaneous perfusion of the distal left anterior descending coronary artery with saline solution under equal physiologic pressures. Slices of the stained heart were incubated with triphenyltetrazolium to identify gross infarct (with histologic confirmation). Total mass of left ventricle, myocardium at risk, and infarct size were measured in each dog. A direct relation was found between the mass at risk and the mass infarcted ($r = 0.84$, $p < 0.001$). Aspirin-treated dogs did not differ from control dogs in percent ventricle at risk (mean ± standard error 37 ± 2 versus 40 ± 2), percent infarct weight/left ventricle (29 ± 3 versus 31 ± 2) or percent infarct weight/weight of ventricle at risk (78 ± 4 versus 77 ± 3). Thus, despite aspirin's ability to inhibit platelet aggregation and to increase epicardial collateral flow by more than 50 percent, aspirin treatment failed to reduce infarct size in this dog model.

Platelets accumulate in the ischemic myocardium of both dogs and primates after experimental coronary arterial occlusion,[1,2] and aspirin has been shown to decrease platelet trapping in the periphery of ischemic myocardium in the dog.[1] Hence, aspirin and other platelet-inhibitory drugs might be beneficial during acute myocardial ischemia by preventing platelet-mediated vascular obstruction and by improving blood flow to the ischemic region. Compatible with this hypothesis are the findings that aspirin reduces electrocardiographic evidence (S-T segment elevation) of acute ischemia[1] and, when administered intravenously in platelet-inhibitory doses to dogs before coronary occlusion, increases epicardial collateral flow by more than 50 percent 4 hours after occlusion.[3] The current study was undertaken to determine whether this potentially beneficial increase in blood flow in dogs is associated with salvage of ischemic myocardium and reduction of infarct size.

Variability in the amount of myocardium lying within the distribution of canine coronary arteries results in significant variation in the mass of infarcted tissue within a group of dogs after coronary occlusion, even when care is taken to ligate the artery at the same anatomic site.[4] The effects of possible infarct-sparing agents on infarct size are thus difficult to assess. Hence, we employed a method to determine myocardial infarct mass relative to the mass of myocardium lying within the distal distribution of the occluded coronary artery, using postmortem staining techniques.

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Methods

Experimental procedure: Thirty-four foxhounds of either sex, weighing 22 to 33 kg, were anesthetized with sodium thiamylal, halothane and nitrous oxide. The animals were intubated and artificially respired with room air. Heart rate and blood pressure were monitored. Under sterile operating conditions, the heart was exposed through a left thoracotomy, and the left anterior descending coronary artery was isolated from surrounding tissue.

Aspirin (*acetylsalicylic acid, U.S.P.*), 1.0 mg/ml, dissolved in a solution of saline and sodium bicarbonate at pH 7.4 to 7.5, was administered intravenously over a 2 minute period to 17 randomly chosen dogs in a dose of 3 mg/kg body weight. This intravenous dose of aspirin has previously been shown to fully inhibit in vitro adenosine disphosphate-induced aggregation of dog platelets and to increase epicardial collateral flow during acute ischemia.[5] Seventeen control dogs received intravenous saline solution, 3 ml/kg. Ten minutes after either aspirin or saline administration, the left anterior descending coronary artery was ligated at a point just distal to the first major diagonal coronary artery. Myocardial ischemia was verified by the immediate appearance of cyanotic, often dyskinetic, myocardium on the anterior surface of the heart in the distal distribution of the occluded artery. The thoracotomy was then closed, and anesthesia discontinued. During the next 3 days each dog received either intravenous aspirin, 3 mg/kg, or saline solution, 3 ml/kg, every 24 hours.

Five dogs in each treatment group died within 72 hours after occlusion. Of these, one dog treated with aspirin and two control dogs had ventricular tachycardia that progressed to ventricular fibrillation and died within the 1st hour after occlusion. The remaining seven dogs died between 24 and 60 hours after occlusion; autopsy studies in these animals demonstrated evidence of myocardial infarction in the distribution of the distal left anterior descending coronary artery and no other apparent cause of death. These 10 dogs are excluded from subsequent analysis.

Preparation of the heart: Seventy-two hours after occlusion, the 24 surviving dogs were given 10,000 units of heparin intravenously and killed with a lethal dose of sodium pentobarbital. The hearts were immediately excised and rinsed. To determine the region of distribution of the left anterior descending coronary artery distal to the occlusion, each isolated heart was suspended from the left and right atria by clamps that occluded all veins entering these chambers. A cannula with a diameter of 1.4 cm was inserted and secured into the aortic root, and another (diameter 1.2 mm) into the left anterior descending coronary artery immediately distal to the site of the initial occlusion (Fig. 1). The aortic root was then perfused with Evans blue solution (1 g/100 ml in saline solution) while the distal left anterior descending coronary artery was perfused with saline solution. Perfusion through both cannulas was performed simultaneously and under equal physiologic pressures (110 mm Hg) to prevent flow of dye from the nonischemic portion of the left ventricle to the ischemic myocardium by way of any collateral channels. Such collateral vessels might have existed before occlusion or developed after occlusion. Separate studies in our laboratory have shown that the decrease in pressure across the 1.2 mm cannula was small at low flow rates (less than 10 mm Hg at flow rates of less than 50 cc/min), so that the perfusion pressures at the tips of both cannulas were comparable.

The result of the myocardial staining procedure was the demarcation of two visually distinct regions of the heart (*Fig. 2A*). The Evans blue solution, perfused through the aortic root, stained all myocardium not supplied by the occluded

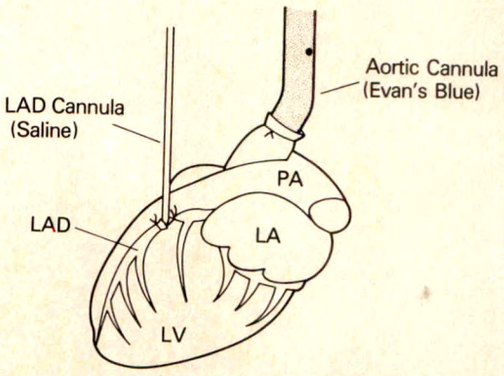

FIGURE 1. Cannulas positioned in the isolated heart for determining the region of distribution of the left anterior descending coronary artery (LAD) distal to the site of occlusion. The aortic cannula was perfused with Evans blue dye while the cannula in the left anterior descending coronary artery was perfused with saline solution. LA = left atrium; LV = left ventricle; PA = pulmonary artery.

portion of the left anterior descending coronary artery a deep blue. The myocardium supplied by this occluded artery, perfused with saline solution, remained unstained. Subsequent experience with fluorescein perfusion of the distal portion of this artery has confirmed that all ventricular myocardium not stained by Evans blue is perfused through the distal left anterior descending artery.[6] This unstained portion of the myocardium was considered potentially at risk of becoming ischemic after occlusion and therefore at risk of infarction. The cannulas were removed, the atria and great vessels were excised and the ventricles were sliced into six or seven parallel "bread-loaf" slices 1 cm thick, each perpendicular to the long axis of the left ventricle (Fig. 2, B and C). The right ventricular free wall of each slice was removed, and each remaining left ventricular slice was weighed and then incubated for 40 minutes in a 1 percent solution of triphenyltetrazolium chloride in phosphate buffer at 40° C by the method of Lie et al.[7] Triphenyltetrazolium staining (Fig. 2D)

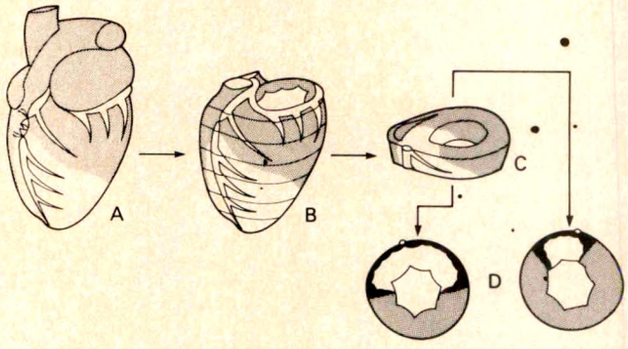

FIGURE 2. Determination of the mass of infarcted myocardium and myocardium at risk of infarction. **A,** result of Evans blue staining showing unstained myocardium "at risk" in the distribution of the left anterior descending coronary artery distal to occlusion. **Heavy stippling** identifies portions of myocardium stained blue. **B,** atria and great vessels removed and ventricles cut into parallel "bread-loaf" slices. **C,** typical mid ventricular bread-loaf slice. **D,** apical and basal surfaces of typical bread-loaf slice of cardiac ventricles after removal of right ventricular free wall and incubation with triphenyltetrazolium chloride. **Solid black areas** identify viable myocardium (stained red by tetrazolium) within the "risk" region.

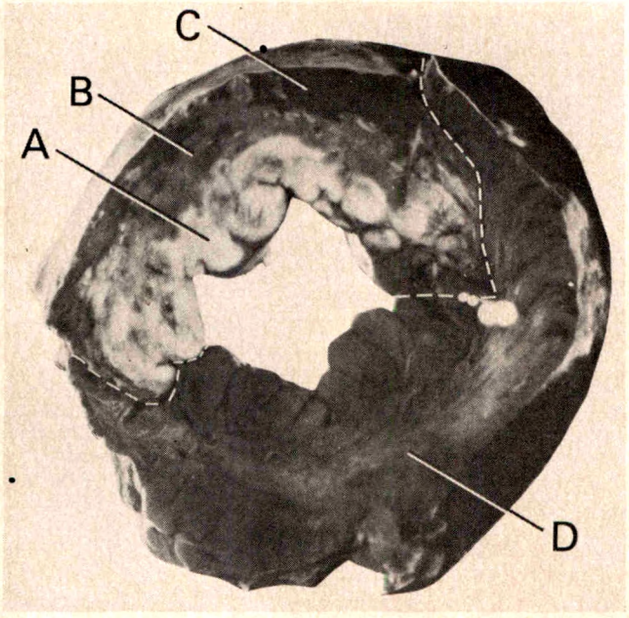

FIGURE 3. Apical surface of a typical bread-loaf slice of the left ventricle after tetrazolium staining (reproduced from a color slide). Within the region at risk, indicated by the area within the **dashed lines,** infarcted tissue is identified as a central white area (A) and a surrounding light pink-stained area (B). Viable myocardium is stained deep red (C). D = normal myocardium outside the region at risk.

discriminated infarcted (unstained and appearing white) from noninfarcted myocardium (stained deep red).[7,8]

Measurement of myocardial infarct size: Color photographs of both surfaces of each slice after incubation with tetrazolium revealed within the region of myocardium at risk three macroscopically distinct areas (Fig 3): a central white area surrounded by an irregular light pink-staining area and a peripheral dark red-staining area. Histologic examination of these areas demonstrated that the white and light pink-stained areas represented infarcted myocardium and that the red-stained area represented normal myocardium (Fig. 4). Normal myocardium within the region at risk, when present, always lay in the lateral and epicardial periphery of the risk region.

Color slides were obtained from both the apical surface and basal surface of each slice, projected onto paper, and traced. The areas of infarction and myocardium at risk for each surface were measured using a video planimetry system[9,10] and expressed as a percent of the total area of the surface. These percent values were averaged for the two surfaces and then multiplied by the mass of the slice to yield the mass of myocardium at risk and the mass of infarct for that slice. This procedure, performed for all six or seven slices and then summed, determined the total mass of the left ventricle, the mass of myocardium at risk of infarction and the mass of infarcted myocardium. The mass of infarcted myocardium was then expressed both as a percent of total left ventricular mass and as a percent of the mass of myocardium at risk of infarction.

Statistical methods: Data were analyzed with Student's *t* test (using paired and unpaired data) and linear regression analysis.

Results

Hemodynamics: Hemodynamic data before and 5 minutes after occlusion of the left anterior descending coronary artery in aspirin-treated dogs did not differ significantly from findings in control dogs (Table I). Paired analysis revealed no significant increase in heart rate after occlusion for either treatment group or for the entire study population. However, both groups had significant decreases in mean femoral arterial pressure after occlusion ($p < 0.05$), which persisted in most ani-

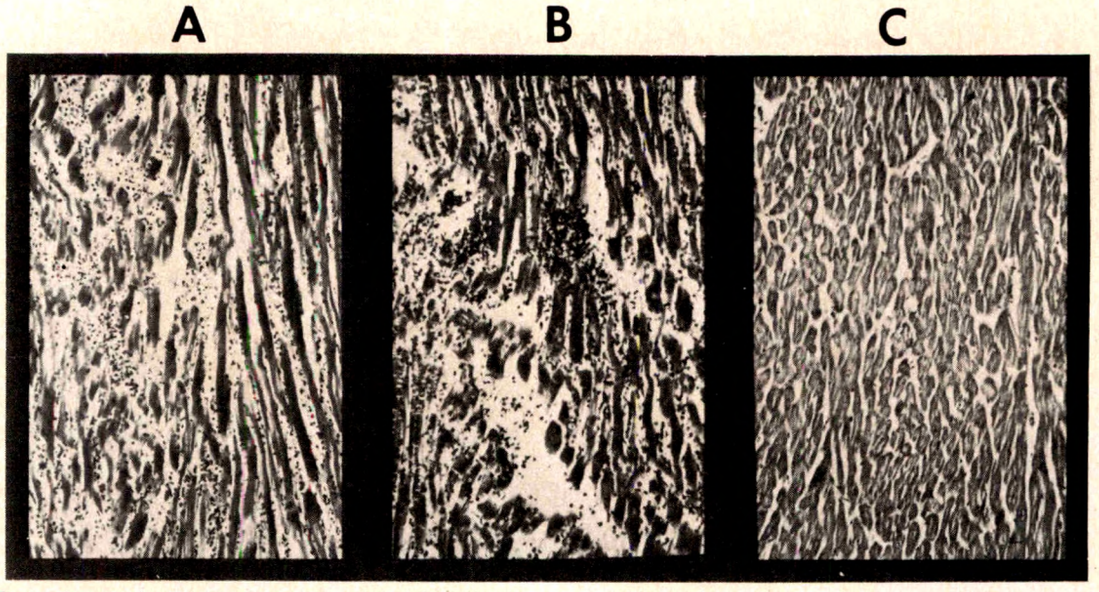

FIGURE 4. Photomicrographs of histologic sections taken from the three areas of the region at risk. **A,** section from white (unstained) area of the risk region corresponding to area A in Figure 3. Coagulation necrosis and polymorphonuclear cell infiltration indicate that this area is infarcted. **B,** section from light pink-stained myocardium corresponding to area B in Figure 3. There is again coagulation necrosis and polymorphonuclear infiltration indicating that this area is histologically identical to the white (unstained) area. **C,** section from deep red-stained myocardium shows normal histologic structure. (Hematoxylin-eosin ×50, reduced by 10 percent.)

mals until the termination of hemodynamic monitoring. Change in heart rate or blood pressure did not correlate with either the mass of infarcted tissue or the mass of myocardium supplied by the left anterior descending coronary artery distal to the occlusion (myocardium at risk), determined by the subsequent staining techniques.

Infarct size: The calculated myocardial infarct mass varied widely in both groups (0.9 to 66.4 g in aspirin-treated dogs and 0.5 to 60.1 g in control dogs) despite careful attempts to ligate the left anterior descending coronary artery at similar anatomic sites in all dogs. Infarct size correlated poorly with total left ventricular mass ($r = 0.14$), but showed excellent correlation with the myocardial mass at risk; infarct size, expressed as a percent of left ventricular mass (Fig. 5), was directly related to the size of the risk region ($r = 0.84$, $p < 0.001$). This was true in both the control group ($r = 0.87$, $p < 0.001$) and the aspirin-treated group ($r = 0.84$, $p < 0.001$). The linear regression equation derived from this relation suggested that dogs with a small region of risk (less than 20 percent of left ventricular mass) would not manifest a myocardial infarction after occlusion. Of the four dogs with a risk region of less than 30 percent of left ventricular mass, three had an infarct mass of less than 2 percent of the left ventricular mass.

A linear relation was not observed between infarcted myocardium and myocardium at risk (Fig. 6), when infarct size was expressed as a percent of the mass of the risk region ($r = 0.39$). Instead, a threshold relation existed, so that three of four dogs with a small risk region (less than 30 percent of the left ventricle) had virtually no infarct, whereas dogs with a larger region at risk (greater than 30 percent of the left ventricle) consistently had a larger infarct (62 to 96 percent) of the region at risks. Because risk regions of less than 30 percent of left ventricular mass would be anticipated to yield a low incidence rate of infarction, the four dogs with such a risk region were excluded from the final analysis. When these four dogs were excluded, the size of the risk region again did not correlate with the percent of the risk region with infarction ($r = 0.36$).

A beneficial effect of aspirin on myocardial infarct size (that is a smaller infarct size than the control value for any given mass of myocardium at risk) would shift the aspirin data points in Figures 5 and 6 in a downward direction. However, the relation between infarct size and risk region (Fig. 5) did not differ between the control and the aspirin-treated groups (slope 1.32 versus 1.74, difference not significant). Moreover, aspirin-treated dogs did not differ significantly from control dogs in total infarct size, infarct size relative to left ventricular mass or infarct size relative to myocardium at risk (Table II). When the four animals with a risk region of less than 30 percent of left ventricular mass were included in a repeated analysis, the findings were unchanged.

Discussion

Role of antiplatelet agents in experimental myocardial infarction: Platelet deposition has been demonstrated in ischemic myocardium during experi-

TABLE I

Hemodynamic Data (mean ± standard error of the mean)

Group	Before Occlusion		5 Minutes After Occlusion	
	Heart Rate (beats/min)	Blood Pressure* (mm Hg)	Heart Rate (beats/min)	Blood Pressure* (mm Hg)
Control	128 ± 5	79 ± 4	132 ± 5	68 ± 4
Aspirin-treated (3 mg/kg)	122 ± 6	79 ± 5	121 ± 5	71 ± 5

* Mean femoral arterial pressure.

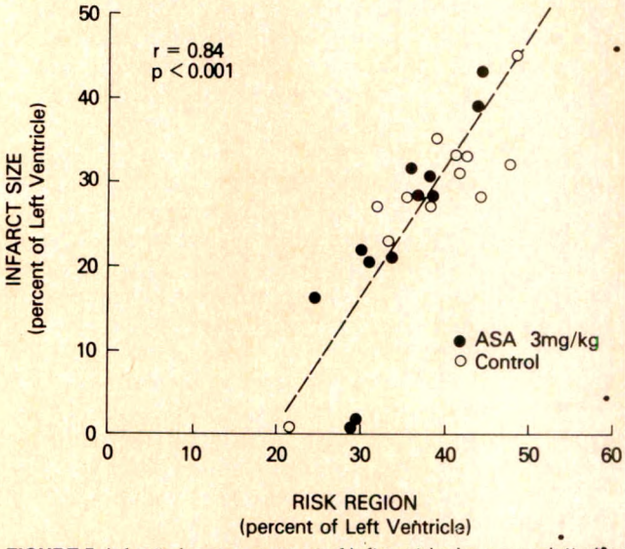

FIGURE 5. Infarct size as a percent of left ventricular mass plotted as a function of the left ventricular region at risk of infarction (myocardial mass lying within the distribution of the left anterior descending coronary artery distal to occlusion). ASA = aspirin-treated; p = probability; r = correlation coefficient.

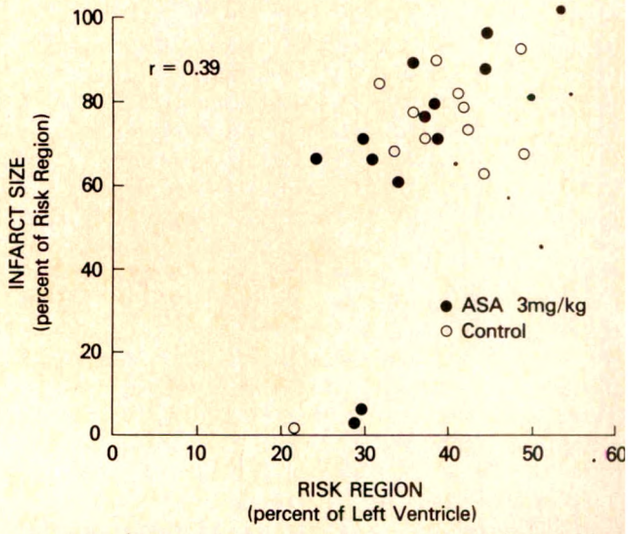

FIGURE 6. Infarct size as a percent of the region at risk plotted as a function of the size of the region at risk. Abbreviations as in Figure 5.

TABLE II

Data on Infarct Size (mean ± standard error of the mean)

Group	LV Mass (g)	Risk Region*		Infarct Mass		
		g	% LV Mass	g	% LV Mass	% Risk Region
Control (n = 11)	123 ± 6	51 ± 4	40 ± 2	39 ± 4	31 ± 2	77 ± 3
Aspirin-treated (n = 9)	120 ± 6	46 ± 4	37 ± 2	36 ± 5	29 ± 3	78 ± 4

* Myocardial mass lying within the distribution of the distal left anterior descending coronary artery.
LV = left ventricular.

mental coronary arterial occlusion in both dogs and primates,[1,2] and pretreatment with aspirin reduces such platelet trapping.[1] Aspirin administration in dogs has also been shown to abolish completely spontaneous cyclic reductions in coronary flow that are associated with platelet aggregates after subtotal occlusion[11] and to reduce the extent of myocardial necrosis induced by epinephrine infusion, which also is associated with platelet aggregation.[12] Aspirin-induced reductions in S-T segment elevations[1] and in the incidence of ventricular fibrillation[13] have been reported in dogs after coronary occlusion. Moreover, aspirin increases collateral flow to the border of ischemic regions in baboons[14] and to the epicardial zone within the ischemic region 4 hours after occlusion of the left anterior descending coronary artery in dogs.[3,5] Finally, ibuprofen, whose effects are similar to those of aspirin in inhibiting prostaglandin synthesis and platelet aggregation, has recently been shown to reduce infarct size in dogs.[15,16]

However, the available evidence does not uniformly demonstrate a beneficial role of aspirin and other antiplatelet agents during acute myocardial ischemia. Ogletree and Lefer[17] found no decrease in either creatine kinase release or S-T segment elevation in cats pretreated with aspirin, and indomethacin was found in dogs to reduce collateral flow[18] and to increase S-T segment elevation[18] and infarct size.[19]

Our study was undertaken to resolve the ambiguities concerning the potential role of aspirin in reducing myocardial infarct size in a canine model of acute infarction. We chose to administer aspirin intravenously in a dose of 3 mg/kg. This dose has previously been shown to inhibit fully canine platelet aggregation and to augment significantly epicardial collateral flow after coronary occlusion; a larger dose (30 mg/kg) did not result in a further increase in collateral flow.[5]

Methodologic problems in determining infarct size: First, we sought to determine the feasibility of comparing infarct sizes in the canine heart. Meaningful quantitative comparison of myocardial infarct size from dog to dog is difficult because the wide variability in the anatomic distribution of the coronary arteries in this species results in considerable variation in the amount of tissue infarcted. Infarct mass in our series ranged from 0.5 to 66.4 g, despite attempts to ligate the left anterior descending coronary artery at a similar anatomic site in each animal. Correction for differences in left ventricular mass did not reduce this variation. Lowe et al.,[4] using in vitro intracoronary latex injections after occlusion of the left circumflex coronary artery, showed that the amount of myocardial necrosis correlates closely with size of the occluded coronary bed. Jugdutt et al.,[19] utilizing in vitro intracoronary injection of barium to define angiographically the distal coronary bed "risk region" 48 hours after occlusion of the left circumflex artery, also noted an excellent correlation between infarct mass and mass of the risk region.

To delineate the myocardium within the distribution of the left anterior descending coronary artery distal to occlusion in our series, Evans blue dye was delivered to the myocardium by way of the aortic root and saline solution was infused, simultaneously and under equal physiologic pressures, at a site just distal to the site of occlusion. The unstained myocardium thus represented the "region at risk" and the myocardium stained blue represented that portion of the heart perfused by vessels unaffected by the occluded artery. The unstained risk region was then "counterstained" by incubation in triphenyltetrazolium chloride, to identify macroscopically the infarcted portion of the risk region. The presence of normal or infarcted myocardium was then confirmed histologically.

Left anterior descending coronary risk regions determined with our method (40 ± 1 percent of the left ventricle) were comparable with the left circumflex coronary risk regions of Lowe et al.[4] and Jugdutt et al.[19] (42 ± 1 percent and 43 ± 4 percent, respectively). However, infarct size in our control dogs was considerably greater (31 ± 2 percent of the left ventricle in our series versus 15 ± 1 percent and 14 ± 2 percent in theirs). These differences may represent methodologic differences from our open chest coronary occlusion technique (Lowe et al. used a coronary arterial reperfusion model, and Jugdutt et al. performed coronary occlusions in closed chest animals), or differences in the in vitro demarcation of the regions at risk. Alternatively, these disparate results may reflect differences in the properties of collateral circulation within the distal left anterior descending and left circumflex coronary arterial beds of the dog. Infarct size (28 ± 2 percent of the left ventricle) in the control group studied by Ribeiro

et al., who utilized occlusion of the left anterior descending artery in open chest dogs,[15] was quite similar to that in our series.

Despite these differences, we found an excellent correlation between infarct mass and mass of the distal left anterior descending coronary risk region, either when both variables were expressed as absolute mass ($r = 0.86$) or when both were expressed as a percent of total left ventricular mass ($r = 0.84$, Fig. 5). From our linear regression equation, risk regions of 20 percent or less of left ventricular mass would be anticipated to contain no infarct. This observation was previously suggested by extrapolation of the data in models of occlusion of the left circumflex coronary artery.[4,19] Our actual data demonstrated that three of four dogs in our series with a risk region of less than 30 percent of left ventricular mass had only tiny islands of infarcted tissue by tetrazolium staining, confirmed histologically, that constituted 0.2 to 1.5 percent of the left ventricle. Presumably, the potential for collateralization of small regions of risk is sufficient to prevent extensive infarction. Aside from these three dogs with a small region of risk, the percent of infarcted muscle within the risk region was extensive, and ranged from 62 to 96 percent.

Explanation for lack of beneficial effect of aspirin on infarct size: Because of the good correlation between infarct mass and mass of myocardium at risk, we believed that this canine model of acute myocardial infarction provided an excellent means of determining whether a given agent can modify infarct size. Our results failed to demonstrate a beneficial effect of aspirin in reducing infarct size (Fig. 5, Table II). The lack of effect of aspirin on overall infarct size is compatible with data demonstrating no decrease in either creatine kinase release or S-T segment elevation in cats treated with oral aspirin (50 mg/kg) before ligation of the left anterior descending coronary artery.[17]

Several explanations may contribute to this lack of beneficial effect. The dose of aspirin we used, 3 mg/kg, fully inhibits platelet aggregation and also augments epicardial collateral flow during acute coronary occlusion.[5] However, the same dose of aspirin also abolishes completely the enhanced coronary flow response to 1.0 and 3.0 mg of intracoronary arachidonic acid,[20] presumably because it inhibits the arachidonic acid-induced synthesis of potent vasodilatory prostaglandins (prostacyclin, for example). It is therefore possible that the initial increases in collateral flow[3,5] and beneficial electrophysiologic effects[1,13] induced by aspirin during acute ischemia are eventually attenuated by inhibition of prostaglandin-mediated vasodilation, so that collateral flow and tissue perfusion are not maintained. Also, in the presence of profound ischemia, modest increases in collateral flow may not be sufficient to maintain myocardial viability. This explanation is compatible with the data of our previous study, in which we found that, although aspirin increased epicardial flow significantly (from 0.19 ± 0.04 to 0.34 ± 0.08 ml/min per g 4 hours after occlusion of the left anterior descending coronary artery), the final flow was only 30 percent of flow in normal nonischemic myocardium.[5]

Thus, despite aspirin's ability to inhibit platelet deposition and augment epicardial collateral flow in the dog, these potentially beneficial actions do not translate into salvage of ischemic myocardium and reduction in infarct size as assessed 72 hours after occlusion.

Acknowledgment

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Regional Myocardial Kinetics of Lidocaine in Experimental Infarction: Modulation by Regional Blood Flow

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The regional myocardial concentration of lidocaine after intravenous bolus administration was studied in the setting of myocardial infarction in 27 dogs utilizing a 24 hour old infarct model. Myocardial levels of lidocaine measured by gas chromatography were related to regional myocardial blood flow measured by radioactive microspheres in the same sample. A highly significant positive linear relation was noted between relative regional myocardial blood flow and lidocaine tissue concentration in animals killed 1 and 3 minutes after the injection of lidocaine ($R^2 = 0.81$ and 0.85, respectively). This positive linear relation was no longer evident at 5 or more minutes after injection of lidocaine. This lack of linear relation resulted from dramatic reductions in myocardial lidocaine concentration in normally perfused zones with much lesser reductions in lower flow zones. Thus the initial distribution of lidocaine after bolus injection is directly proportional to myocardial blood flow within the first 3 minutes of injection. Thereafter, the washout of lidocaine appears to be the dominant factor in myocardial distribution.

After acute myocardial infarction, drug delivery to the ischemic ventricular zone may be affected by the same pathophysiologic process—namely, a decrement in regional blood flow—that initially resulted in the infarct. Conventional monitoring of therapeutic efficacy based solely on plasma or serum drug levels would not provide insights into such a flow-related regional phenomenon and could lead to ineffective management. Such a situation would be particularly critical in relation to delivery of antiarrhythmic drugs. In this instance, failure to achieve an adequate drug concentration in a low flow arrhythmogenic zone of ventricular myocardium could result in lack of abolition of potentially lethal cardiac arrhythmias.[1,2]

This study examines, in the setting of experimental infarction, the effects of decreased regional myocardial blood flow on regional myocardial lidocaine kinetics at various times after intravenous bolus injection of the drug. Utilizing a 24 hour old canine myocardial infarct model, tissue lidocaine levels measured by gas chromatography were related to regional myocardial blood flow measured by the radioactive microsphere technique in the same samples.

Methods

Experimental preparation: A total of 27 mongrel dogs of either sex weighing between 20 to 30 kg were studied. Following anesthesia with intravenous sodium pentobarbital (30 mg/kg), acute anterior wall myocardial infarction was induced by a closed chest catheter plug embolization technique described previously.[3] Briefly, a 7 Sones catheter was advanced through the right carotid artery into the aortic root and positioned subselectively under fluoroscopic control in the orifice of the left anterior descending coronary artery. A radiopaque plug made of catheter material and impaled on the distal end of a guide wire previously placed within the catheter was then dislodged into the coronary artery. This was

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achieved by pulling back on the proximal end of the guide wire. The plug usually occluded the distal third of the coronary artery at the point of origin of the last large diagonal branch from the anterior descending artery.

Lidocaine groups: After infarction, the dogs were allowed to recover for 24 hours. The animals with 24 hour old infarcts were then reanesthetized and a lateral thoracotomy was performed. A cannula was placed in the left atrial appendage for the injection of radioactive microspheres necessary for measurement of relative regional myocardial blood flow.[5,6] Each dog then received lidocaine, 1.5 mg/kg, as an intravenous injection over 1 minute through a peripheral vein. The dogs were separated into six groups of four to five animals. The groups were defined by the time after completion of the lidocaine injection at which the dogs were killed. These times were 1, 3, 5, 15, 30 and 120 minutes after the administration of the total lidocaine dose. Before termination of each experiment, 1.1 to 2.2 × 10^6 radiolabeled microspheres (strontium-85) 15 ±5μ in diameter (3M Corporation) were injected by way of the left atrial cannula. The dogs were killed and the hearts rapidly removed. Blood samples from a different peripheral vein were also obtained immediately before the dogs were killed.

Myocardial tissue samples: Approximately 12 full thickness myocardial samples were obtained from the infarcted portion of the left ventricle. Six to eight additional normal left ventricular tissue samples were obtained from the normal ventricular region supplied by the circumflex coronary artery remote from the infarcted area. Tissue samples were blotted to remove blood from the tissue. Samples from the normal zone were obtained immediately after removal of the heart as well as at the end of the tissue-harvesting procedure (10 dogs, studied at 1 and 3 minutes). Comparison of lidocaine data in these normal tissues allowed assessment of any possible postmortem leakage of the drug from myocardial tissue during the period of tissue dissection before the sample was obtained and placed in a test tube. All myocardial samples were divided in half, representing endocardial and epicardial portions and were weighed. Sample weight ranged from 0.4 to 3.5 g. Samples were then placed in scintillation vials containing 4 cc of 10 N sodium hydroxide per gram of tissue (for subsequent homogenization) and the radioactivity was measured in an automated gamma counter (Beckman 8000 gamma counter, Irvine, California). After gamma counting for microsphere activity the tissue was homogenized using an ultrasonic cell disrupter (model WD-225-R Heat Systems-Ultrasonic Inc., Plainview, New York) and the sample frozen until analyzed subsequently with gas chromatography. Blood samples were centrifuged, and the plasma saved was frozen for lidocaine determination.

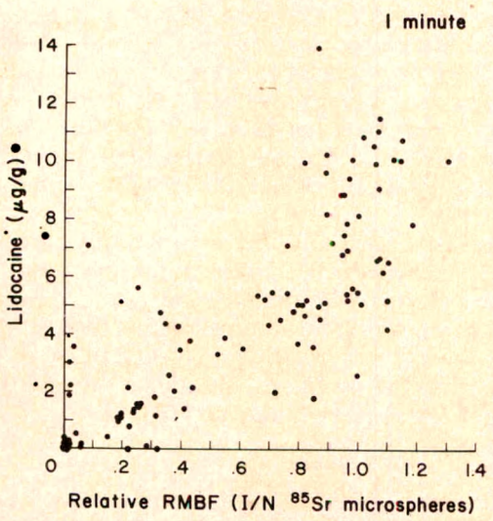

FIGURE 1. Relation between regional myocardial concentration of lidocaine (micrograms per gram of tissue) and relative regional myocardial blood flow (RMBF) expressed as a ratio of radioactivity in the infarct (I) zone compared with the mean value of all normal (N) myocardial samples in each animal 1 minute after intravenous lidocaine injection. Statistical analyses of the data are found in the text. ^{85}Sr = strontium-85.

Lidocaine assay: Lidocaine in blood and tissues was measured with the technique of Benowitz and Rowland.[7] Homogenized tissue samples were processed in the same manner as the plasma samples. The technique consists of the following steps: Plasma or tissue homogenate, 1 to 2 ml, was placed in a screw-capped centrifuge tube; then 0.5 ml of 2-diethylaminoacetanilide (Kodak) was added. After the addition of 7 ml of distilled ether, the solution was shaken for 1 minute and centrifuged (room temperature) at 3,000 rpm. The ether layer was transferred to a conical tube containing 0.2 ml of 0.1N hydrochloric acid. After manual shaking for 1 minute, the mixture was centrifuged at 3,000 rpm for 10 minutes and the ether layer discarded. Then 0.1 ml of 0.5N sodium hydroxide was added for alkalinizing the solution and 50 μ-liters of carbon disulfide was also added. After vortexing and centrifuging, the lower carbon disulfate phase was carefully sampled with a Hamilton syringe and 2 μliters injected into the gas chromatograph (GC 6AM Shimadzu, Columbia, Maryland). The ratio of lidocaine to the internal standard was calculated by comparison of the area under the curve of the respective peaks and the concentration was determined with reference to the standard curve. Standard curves were prepared every day from plasma or tissue, or both, thus allowing for compensation for any incomplete recovery from samples from cardiac tissue or plasma. Linear standard curves were obtained with similar ratios for water, plasma and cardiac tissue. The lower limit of sensitivity of the assay is 0.01 μg/ml, well below the concentrations obtained in this study. Homogenized cardiac tissue and plasma from control animals not receiving lidocaine showed no peak that might interfere with measurement of lidocaine or the internal standard. The coefficient of variability for the same samples was approximately 10 percent.

Statistical analysis: Data from these studies are expressed as absolute concentrations of lidocaine in micrograms/gram of myocardial tissue or micrograms/milliliter of serum. The infarct to normal ratio for the microspheres represents a relative measure of regional myocardial blood flow and is a ratio of activity in the infarct zone sample as compared with the mean value of all normal samples in that animal.

Data are expressed as mean ± standard error of the mean. The analysis of variance and multiple regression was carried out using PROG GLM in the SAS satistical package.[8] Differences between groups were determined with Student's *t* test; a value of $p < 0.05$ was considered significant.

Results

Relation between regional myocardial flow and lidocaine concentration (Fig. 1): A highly significant relation was noted between relative regional myocardial blood flow and lidocaine myocardial concentration in

animals killed 1 and 3 minutes after the lidocaine bolus injection. The relation was linear (R^2 0.83, 0.82, 0.59, 0.94 and 0.68, respectively, for the individual dogs killed at 1 minute and 0.48, 0.82, 0.85, 0.84 and 0.81, respectively, for those killed at 3 minutes. Pooling data of each time period into a single multiple regression, allowing for differences among dogs and between the epicardium and endocardium, gave a multiple correlation coefficient of $R^2 = 0.81$ at 1 minute and $R^2 = 0.85$ at 3 minutes. It should be noted that Figure 1 suggests a curvilinear relation between blood flow and lidocaine concentration. This was not apparent when the association was considered within dogs. The differences in trend among dogs are largely responsible for this phenomenon. Furthermore, at 1 and 3 minutes after injection of lidocaine, there were statistically significant decrements in myocardial lidocaine concentrations noted even at modest (60 to 80 percent of normal) blood flow reductions. These same significant decrements were also noted at lower blood flow ranges (Table I, Fig. 2) ($p < 0.01$) (Student's t test). Analysis of variance revealed that for both 1 and 3 minutes, relative blood flow was the single largest contributor to the sums of squares explained by the model, whereas for 2 hours the greatest source of variability was among dogs. At all three times there were significant differences in the effect of flow on lidocaine concentration among dogs. For 1 and 3 minutes the associations were all positive and highly significant but for 2 hours they were mixed, three dogs showing a fairly strong negative association and one a modest positive association with relative blood flow.

Normal flow zones versus low flow zones (Table I, Fig. 2): There was a rapid and dramatic reduction in myocardial lidocaine concentration with time noted in the normal flow zones. The reduction was substantially less in the lower flow zones, so that by 5 minutes after lidocaine injection there was no difference between concentrations of lidocaine in the lowest flow zone (less than 20 percent of normal) and in the normal zones. Thus, the initial distribution of lidocaine after bolus injection was directly proportional to regional blood flow. Shortly after distribution, the washout of lidocaine seemed to be the dominant factor in determining subsequent myocardial distribution.

Endocardial versus epicardial zones: There was a significant increase in endocardial lidocaine levels as compared with epicardial levels in normal flow zones at 1 minute, whereas the infarcted zones showed a trend to higher levels in the epicardium (p-not significant [NS]) (Table II). These findings were consistent with a greater decrement in flow in the endocardium than in the epicardium. As might be expected, on the basis of a flow-related deposition, this phenomenon was most apparent 1 minute after injection, and statistically significant trends were not apparent from 3 minutes after injection onward.

Infarcted versus normal myocardium: No simple relation existed between lidocaine myocardial and blood levels in various zones of infarcted and normal myocardium (Table III). The lidocaine myocardial blood ratio remained relatively constant in normal myocardium throughout the period of study, whereas it changed dramatically in zones of decreased flow, with a lower ratio during the initial 3 minutes after injection and a subsequent rise thereafter. These data indicate the difficulties of correlating lidocaine blood levels to local response in the first few minutes after bolus injection.

A comparison of lidocaine levels in normal myocardium harvested at the beginning and the end of tissue dissection period revealed comparable lidocaine levels (8.86 ± 0.44 μg/g [n = 29] versus 8.11 ± 0.41 μg/g [n = 28] [p-NS]; and 5.1 ± 0.32 μg/g [n = 31] versus 5.7 ± 0.6 μg/g [n = 23] [p = NS] at 1 and 3 minutes, respectively). Thus there was no efflux of lidocaine from the myocardial samples occurring during the time of tissue harvesting.

Discussion

Regional myocardial lidocaine pharmacokinetics: Our study indicates that after intravenous bolus injection, lidocaine distribution within the myocardium is dependent on regional myocardial blood flow. A spectrum of patterns of regional lidocaine pharmacokinetics can be distinguished, based on regional myocardial blood flow after infarction. At one extreme, in normally perfused myocardium, there is rapid equilibration with the blood. Lidocaine tissue levels in the normally perfused myocardium present the highest regional concentrations and peak early (at 1 minute after bolus administration. A rapid increase in lidocaine tissue levels is followed by a rapid reduction in lidocaine concentration. At the other end of the spectrum, lidocaine tissue levels in severely hypoperfused myocardium equilibrate more slowly, peak later than the well perfused compartment and have a delayed decline of lidocaine. Intermediate blood flow regions present intermediate patterns of lidocaine influx and efflux. These differences between compartments are most evident within the first 5 minutes after lidocaine bolus administration. After this distribution phase, lidocaine equilibrates in both compartments and declines in parallel with blood levels. Generally there are no differences in patterns of lidocaine kinetics between endocardium and epicardium that are independent of blood flow.

Effect of bolus injection versus constant infusion of lidocaine: Several aspects of this study are of interest. Our data were obtained entirely after bolus injection. Bolus injections are particularly useful to study the patterns of distribution of drugs in relation to time and blood flow. Blood flow is a major determinant of tissue distribution for many drugs. This was recently shown for lidocaine by Benowitz et al.[9] using a perfusion model. These relations between blood flow and drug distribution are of obvious importance in myocardial infarction. The studies of these relations cannot be obtained using constant infusions, although this is the most common way of administering lidocaine to patients.

Data from bolus injection are in contrast to recent observations[10] from our laboratory involving lidocaine

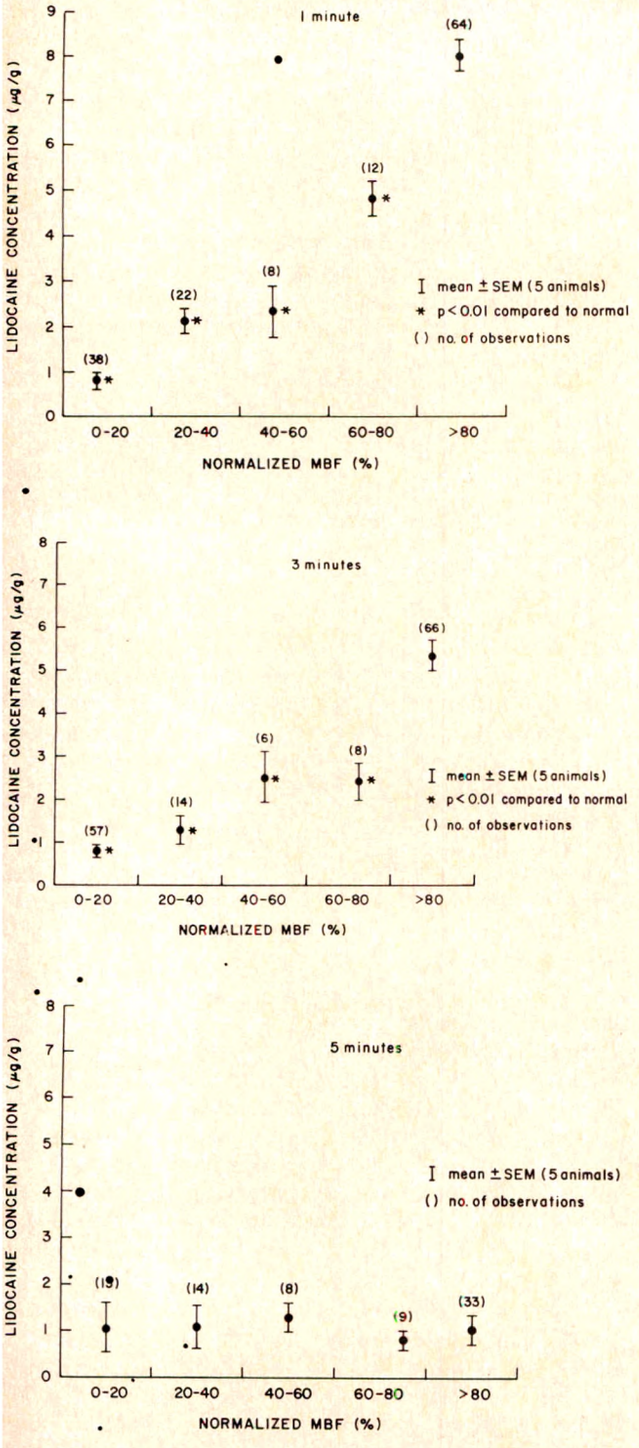

FIGURE 2. Regional myocardial concentration of lidocaine (micrograms per gram of tissue ± standard error of the mean [SEM]) expressed as a function of regional myocardial blood flow (MBF), as measured by the radioactive microsphere technique. Data for 1 minute and 3 and 5 minutes are presented in the **top, middle** and **bottom** panels, respectively. The data are clustered into five groups depending on relative regional myocardial blood flow in the tissue sample. The number of samples corresponding to each flow zone is given in parentheses. Statistical analysis was made by comparing lidocaine concentration in each flow group with the control lidocaine concentration in areas with greater than 80 percent regional myocardial blood flow. Note that lidocaine in the ischemic section differed significantly at 1 and 3 minutes but not at 5 minutes.

constant infusion in which low blood flow zones in ischemic myocardium reached concentrations of lidocaine approximately 40 percent of the levels reached in normal myocardium. After lidocaine infusion of 35 μg/kg per min, a tissue concentration of 3.5 μg/g of lidocaine was found in the normal tissue and of 1.2 μg/g in the most hypoperfused tissues with flows lower than 0.2 ml/min per g. In contrast, with bolus injection lidocaine concentration in low blood flow zones was only 10 percent of that in the normal zones at the peak of blood level at 1 minute. This relatively higher concentration of lidocaine in low blood flow zones during constant infusions probably represents the differences in kinetics between the bolus and constant infusions.

Similar observations were made by Wenger et al.[11] *using a constant infusion of procainamide.* They studied the relation of procainamide and myocardial blood flow during acute ischemia in a canine model. Procainamide was administered as a continuous infusion over 4 hours to what was presumed to be a steady state and the drug tissue levels were measured using a radiochemical combustion technique in which procainamide concentrations were determined from activity collected in the form of carbon-14 carbon dioxide. Myocardial levels of procainamide were maximal in regions with more than 40 percent of normal regional myocardial blood flow. Below this blood flow level, there was a persistent decrement in procainamide levels. However, even in zones with less than 10 percent of normal blood flow, procainamide concentrations were 40 percent of normal as in our results. The reasons for this concentration against flow in the infarcted myocardium as well as the equilibration of lidocaine tissue levels after 30 minutes seen in our study are unclear. However, we can speculate that the mechanisms for lidocaine accumulation in ischemic myocardium may be related to the local properties of the ischemic myocardium. Increased residence time, binding of the drug to molecules such as phospholipids from cell membranes that have been disrupted as a result of ischemia and necrosis, altered metabolism of the drug in the infarcted area and markedly delayed efflux out of the infarcted area may be responsible for this phenomenon.

Methodologic considerations: Several aspects of the model used in our study deserve comment. A 24 hour infarct model was employed. At this particular time, myocardial blood flow is relatively stable and one would not expect intra-study differences in regional flow based on changing patterns of collateral blood flow.[12] From a methodologic standpoint, measurements of flow and measurements of tissue drug level were obtained using two different techniques applied to the same sample. The blood flow measurement was made with radioactive microspheres, whereas the drug myocardial level was assessed with gas chromatography. Therefore, a single sample did not have to be subdivided before analysis to obtain portions of tissue for independent measurement of flow and drug levels. Although attempts were made to remove blood from the myocardial samples by tissue blotting, it is probable that not all

TABLE I

Regional Myocardial Lidocaine Concentration (μg/g, mean ± SEM) As a Function of Relative Regional Myocardial Blood Flow

Interval After Bolus Injection of Lidocaine (min)*	Relative Regional Myocardial Blood Flow†				
	<0.20	0.20–0.40	0.40–0.60	0.60–0.80	>0.80
1	0.87 ± 0.18 (n = 38)	2.1 ± 0.34 (n = 22)	2.33 ± 0.57 (n = 8)	4.84 ± 0.39 (n = 12)	7.98 ± 0.33 (n = 64)
3	0.789 ± 0.10 (n = 57)	1.14 ± 0.28 (n = 14)	2.51 ± 0.61 (n = 6)	2.38 ± 0.4 (n = 8)	5.36 ± 0.30 (n = 66)
5	1.07 ± 0.17 (n = 13)	1.09 ± 0.18 (n = 14)	1.32 ± 0.39 (n = 8)	0.82 ± 0.20 (n = 9)	1.02 ± 0.17 (n = 33)
15	0.24 ± 0.09 (n = 7)	0.366 ± 0.04 (n = 12)	0.60 ± 0.04 (n = 22)	0.77 ± 0.07 (n = 16)	0.98 ± 0.10 (n = 38)
30	0.28 ± 0.04 (n = 25)	0.20 ± 2.04 (n = 25)	0.28 ± 0.06 (n = 21)	0.21 ± 0.12 (n = 6)	0.31 ± 0.04 (n = 35)
120	0.22 ± 0.04 (n = 31)	0.26 ± 0.08 (n = 10)	0.17 ± 0.05 (n = 10)	0.23 ± 0.04 (n = 11)	0.20 ± 0.06 (n = 43)

* Refers to time dogs were killed after intravenous bolus infusion of lidocaine. † Relative regional myocardial blood flow assessed with radioactive microspheres (1.0 = 100 percent control activity).

TABLE II

Regional Myocardial Lidocaine Concentration (μg/g, mean ± SEM) in Endocardium and Epicardium As a Function of Relative Regional Myocardial Blood Flow

Time After Bolus Injection of Lidocaine (min)*	Relative Regional Myocardial Blood Flow†									
	<0.20‡		0.20–0.40		0.40–0.60		0.60–0.80		>0.80	
	Endo	Epi	Endo	Epi	Endo	Epi	Endo	Epi	Endo	Epi
1	0.71 ± 0.18 (n = 30)	1.18 ± 0.5 (n = 8)	2.02 ± 0.4 (n = 9)	2.16 ± 0.5 (n = 13)		2.33 ± 0.51 (n = 8)	5.46 ± 0.51 (n = 3)	4.64 ± 0.43 (n = 9)	8.85 ± 0.46 (n = 29)	7.26 ± 0.44 (n = 35)
3	0.62 ± 0.10 (n = 38)	1.13 ± 0.18 (n = 19)	1.28 ± 0.48 (n = 4)	3.36 ± 2.2 (n = 10)	2.63 ± 1.9 (n = 2)	2.46 ± 0.55 (n = 4)		2.38 ± 0.4 (n = 8)	5.62 ± 0.41 (n = 29)	5.15 ± 0.43 (n = 37)
5	1.00 ± 0.17 (n = 12)	1.94 (n = 1)	1.02 ± 0.26 (n = 9)	1.23 ± 0.24 (n = 5)	0.52 ± 0.23 (n = 3)	1.80 ± 0.51 (n = 5)	0.27 (n = 1)	0.88 ± 0.21 (n = 8)	1.27 ± 0.31 (n = 14)	0.83 ± 0.79 (n = 19)
15	0.24 ± 0.11 (n = 6)	0.25 (n = 1)	0.37 ± 0.06 (n = 9)	0.35 ± 0.06 (n = 3)	0.61 ± 0.06 (n = 7)	0.59 ± 0.04 (n = 15)	0.95 ± 0.04 (n = 6)	0.67 ± 0.09 (n = 10)	1.09 ± 0.16 (n = 19)	0.87 ± 0.12 (n = 19)
30	0.28 ± 0.05 (n = 21)	0.25 ± 0.11 (n = 4)	0.20 ± 0.08 (n = 12)	0.20 ± 0.02 (n = 13)	0.35 ± 0.90 (n = 5)	0.27 ± 0.07 (n = 16)	0.31 ± 0.22 (n = 2)	0.16 ± 0.16 (n = 4)	0.33 ± 0.08 (n = 15)	0.29 ± 0.05 (n = 20)
120	0.22 ± 0.05 (n = 19)	0.22 ± 0.09 (n = 12)	0.29 ± 0.13 (n = 6)	0.23 ± 0.09 (n = 4)	0.19 ± 0.06 (n = 7)	0.14 ± 0.08 (n = 3)	0 (n = 1)	0.25 ± 0.12 (n = 10)	0.25 ± 0.12 (n = 20)	0.15 ± 0.05 (n = 23)

* Refers to time dogs were killed after intravenous bolus infusion of lidocaine. † Relative regional myocardial blood flow as assessed with radioactive microspheres (1.0 = 100% control activity).
Endo = endocardium; Epi = epicardium; SEM = standard error of the mean.

TABLE III

Myocardial to Blood Lidocaine Ratios (± SEM) As a Function of Relative Regional Myocardial Blood Flow*

Time After Bolus Injection of Lidocaine (min)*	Relative Regional Myocardial Blood Flow				
	<0.20‡	0.20 − 0.40	0.40 − 0.60	0.60 − 0.80	>0.80
1	0.10 ± 0.04 (n =38)	0.32 ± 0.06 (n = 22)	0.39 ± 0.18 (n = 8)	0.87 ± 0.18 (n = 12)	0.95 ± 0.11 (n = 64)
3	0.21 ± 0.04 (n = 57)	0.19 ± 0.06 (n = 14)	0.31 ± 0.08 (n = 6)	0.23 ± 0.03 (n = 8)	1.06 ± 0.12 (n = 66)
5	0.77 ± 0.11 (n = 13)	0.76 ± 0.09 (n = 13)	0.91 ± 0.21 (n = 8)	0.61 ± 0.11 (n = 9)	0.78 ± 0.09 (n = 33)
15	0.06 ± 0.23 (n = 5)	0.68 ± 0.07 (n = 11)	1.03 ± 0.07 (n = 21)	1.40 ± 0.07 (n = 14)	1.89 ± 0.14 (n = 32)
30	0.96 ± 0.15 (n = 24)	0.74 ± 0.15 (n = 23)	1.12 ± 0.22 (n = 21)	0.83 ± 0.51 (n = 5)	1.21 ± 0.18 (n = 31)
120	1.70 ± 0.42 (n = 30)	2.35 ± 0.78 (n = 10)	0.49 ± 0.20 (n = 10)	0.81 ± 0.31 (n = 11)	0.40 ± 0.08 (n = 42)

* Values are mean ± standard error of the mean (SEM) of ratios of μg/g of lidocaine in tissue to μg/ml of lidocaine in serum. † Refers to time dogs were killed after intravenous bolus infusion of lidocaine; ‡ Relative regional myocardial blood flow as assessed with strontium-85 microspheres (1.0 = 100 percent control activity).

blood was removed. Therefore, the myocardial lidocaine level may, in a small part, be a function of residual blood activity as well as of tissue drug concentrations. Nevertheless, these data do represent delivery of drug to a given myocardial region.

Relation between tissue levels of lidocaine in ischemic tissue and antiarrhythmic efficacy: This relation is uncertain. Kupersmith et al.[13] pointed out the importance of studying the delivery of lidocaine to understand lidocaine's antiarrhythmic effect. These investigators explained some of lidocaine's electrophysiologic effects in ischemic myocardium by the time course of drug delivery to deep ischemic layers of myocardium. Our finding that lidocaine may exhibit significant delay in reaching deep layers of myocardium are in agreement with this explanation. However, this may vary depending on the model utilized and the time of the study after infarction.

The demonstration of altered tissue distribution of an antiarrhythmic drug represents a first step toward a more detailed study of the interactions of regional pharmacokinetics and pathophysiology. Drug tissue levels must be related to regional electrophysiologic variables to assess the therapeutic efficacy or lack thereof resulting from a flow-related distribution of the drug. Therapeutic effectiveness of an antiarrhythmic agent conceivably may occur even in the presence of an altered regional tissue distribution. Alternatively, the major focus of antiarrhythmic activity of the drug may reside in regions other than the ischemic myocardium, such as the central nervous system or the peripheral autonomic nervous system.

Clinical implications: Experimental electrophysiologic studies in dog models have suggested that arrhythmias may be generated in Purkinje tissues and nonhomogeneous infarcted or ischemic myocardium, or both.[1,2,14,15] These areas of myocardium are the likely sites of action of antiarrhythmic drugs. Giardina et al.[15] proposed that antiarrhythmic drugs such as procainamide may have their site of action in a slow equilibrating low blood flow compartment. Our results with lidocaine show that in poorly perfused myocardium there is a significant lag of time until maximal tissue concentration is reached and thereafter there also is a more gradual decrease. These observations also may support the hypothesis of Giardina et al. as applied to another antiarrhythmic agent.

Our data also are relevant to the clinical observation that lidocaine effect is delayed and lasts longer than expected when blood levels are analyzed following a bolus injection.[16] In addition, they also explain the early discrepancies in effective therapeutic blood levels found after bolus and constant infusions.[16] Although a constant infusion partially overcomes the effect of blood flow on regional lidocaine distribution, drug accumulation in low flow zones may be significantly delayed. Our study supports the recommendation by Bigger[17] of the use of an initial bolus injection of lidocaine together with the double infusion to avoid the initial delay seen with double infusion alone.

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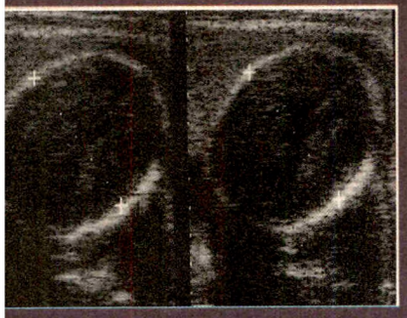

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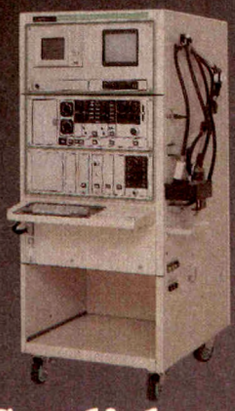

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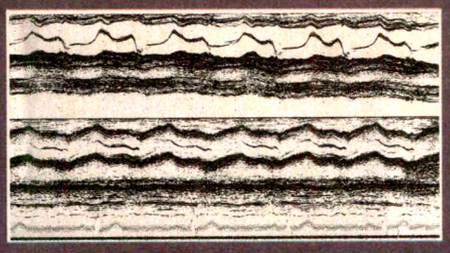

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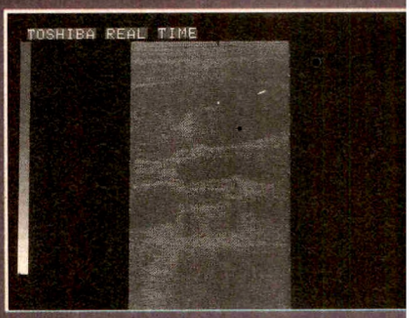

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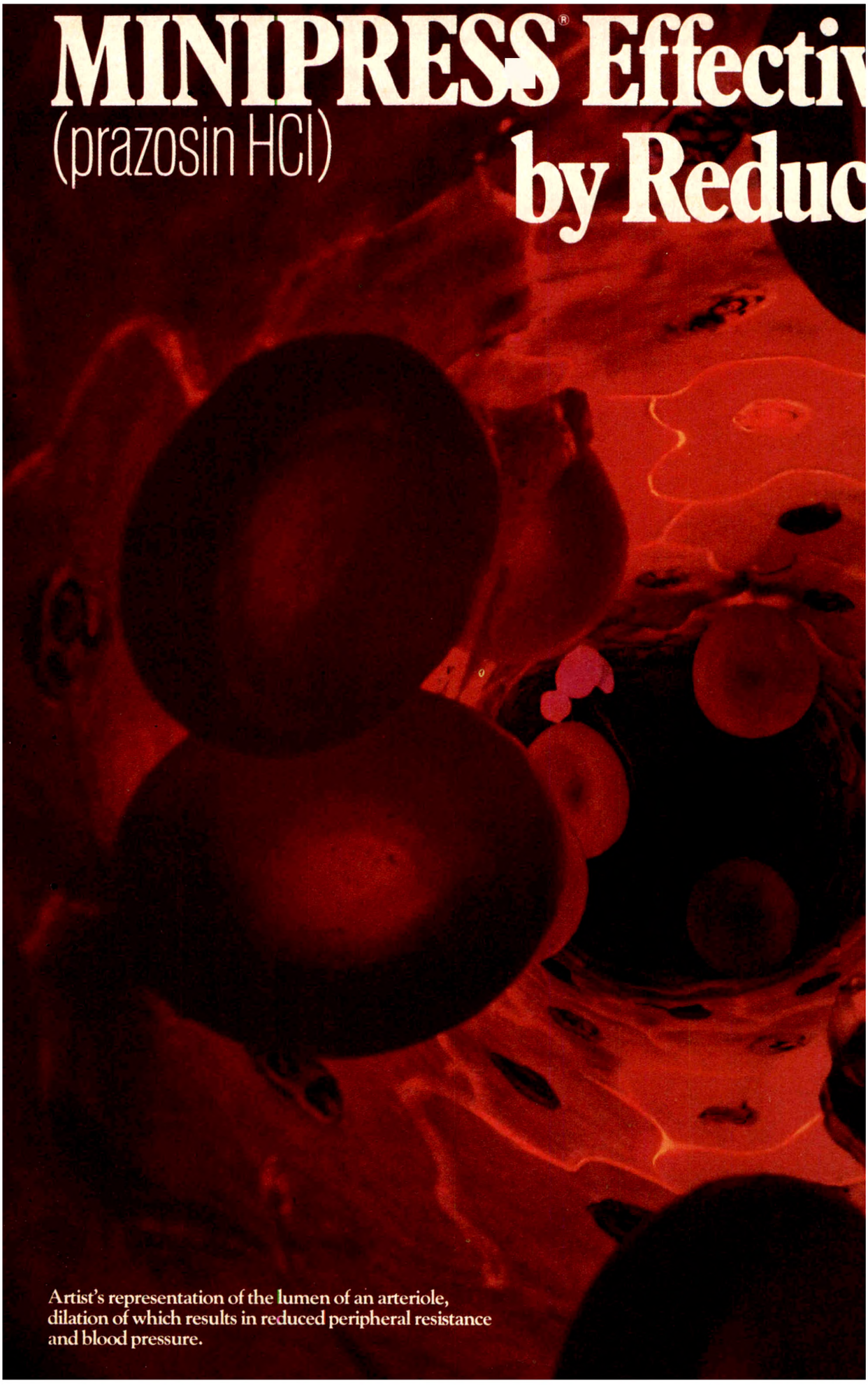
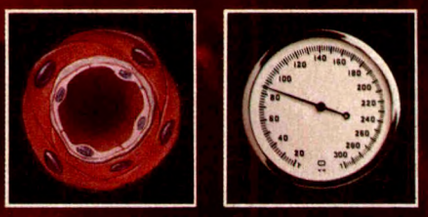


Artist's representation of the lumen of an arteriole, dilation of which results in reduced peripheral resistance and blood pressure.

Controls Hypertension Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
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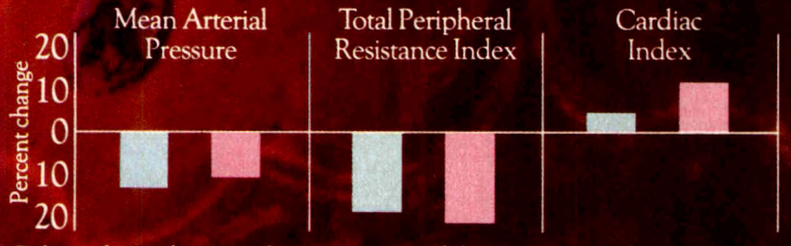
...and Maintains These Effects Over the Long Term



Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen[1]

Rest Exercise

MINIPRESS®

(prazosin HCl)

Capsules 1 mg, 2 mg, 5 mg

Please see Brief Summary on last page.

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MINIPRESS
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

- **Effectively lowers elevated blood pressure by reducing peripheral resistance.**
- **Maintains cardiac output** which allows patients to maintain an active life style.
- **Maintains renal blood flow and glomerular filtration rate** so it can be used effectively even in patients with renal impairment.
- **Not a CNS agent** so patients experience few of the troublesome CNS side effects that impair their quality of life.
- **Cardiovascular response to exercise is preserved** so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- **A small percentage of patients** have experienced orthostatic hypotension and syncope.

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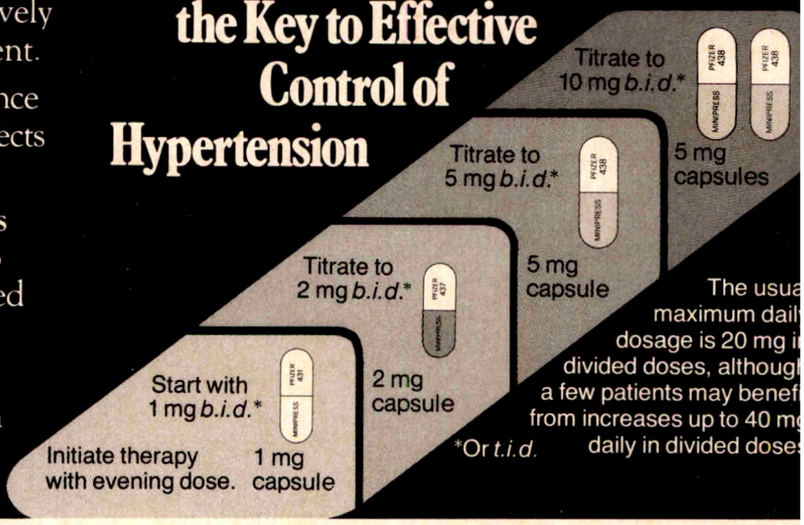

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.

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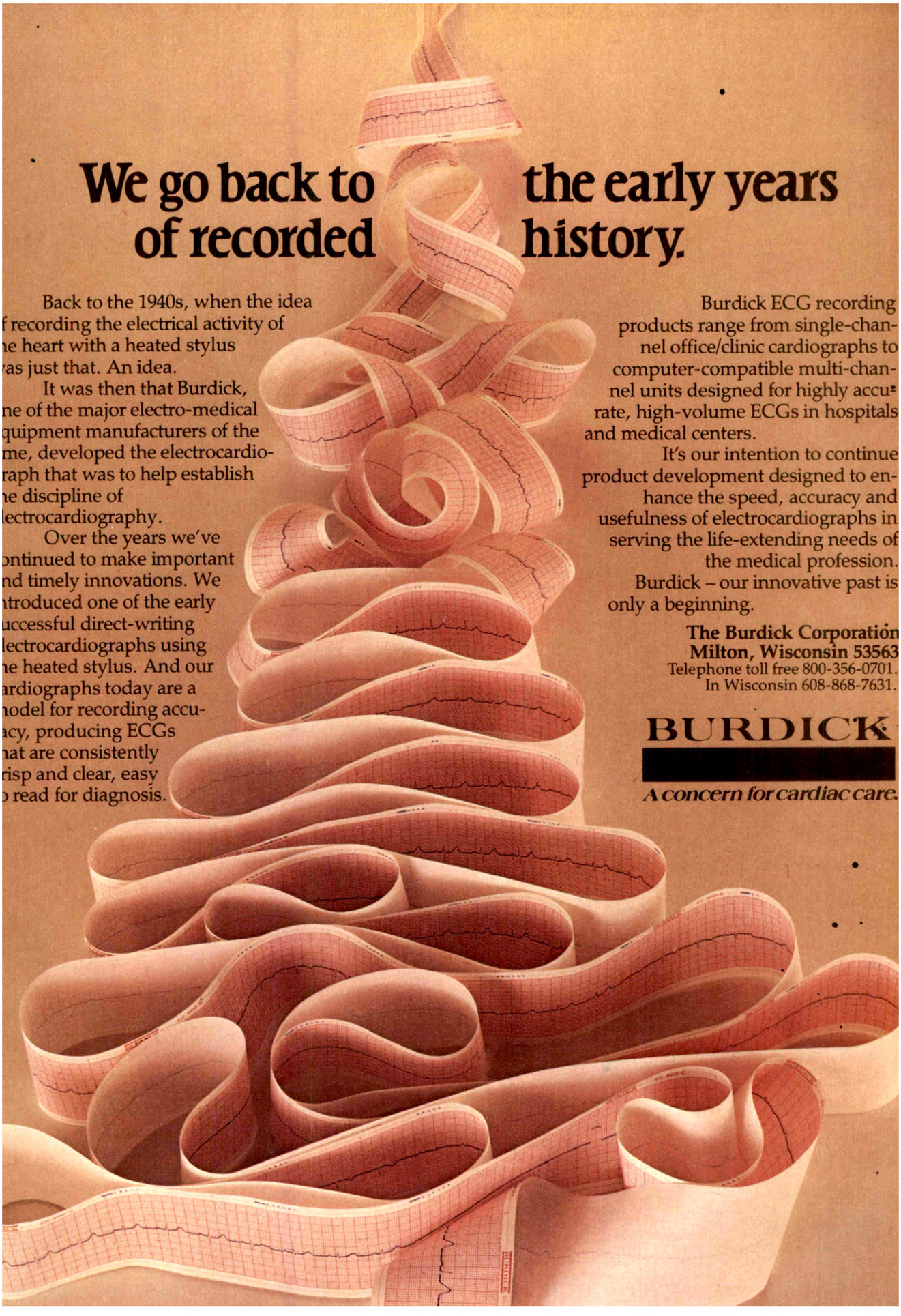

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CURRENT DRAIN		Depends on parameter settings. At standard program: 100% stim. approx. 20 μA; Inhibited approx. 5 μA
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	BASIC RATE	20% drop from programmed value. Occurs a few months after the test rate of 85 imp/min has been passed
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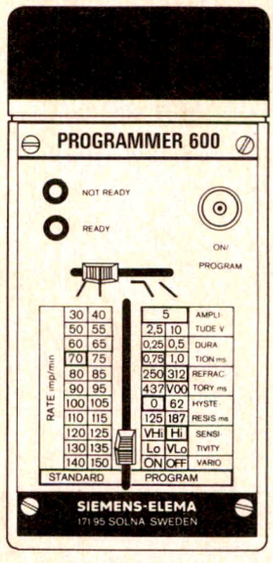

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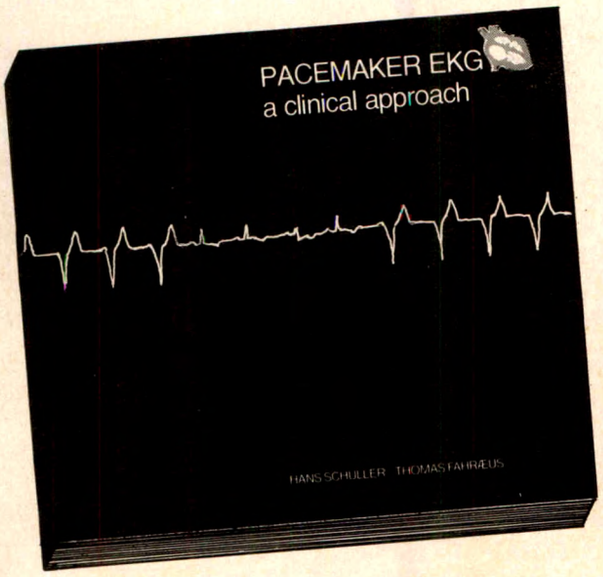

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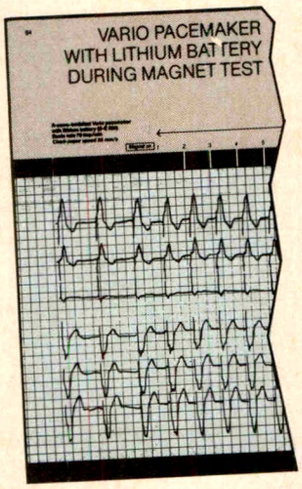
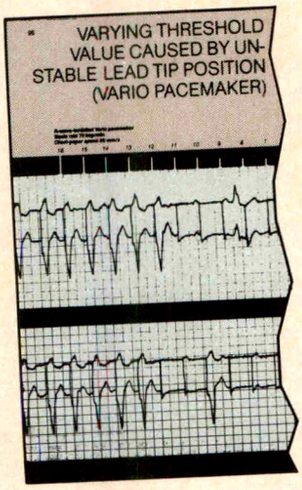


Illustration No. 40, "Different Pacemaker Types and Functions," page 64.



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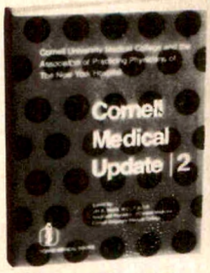

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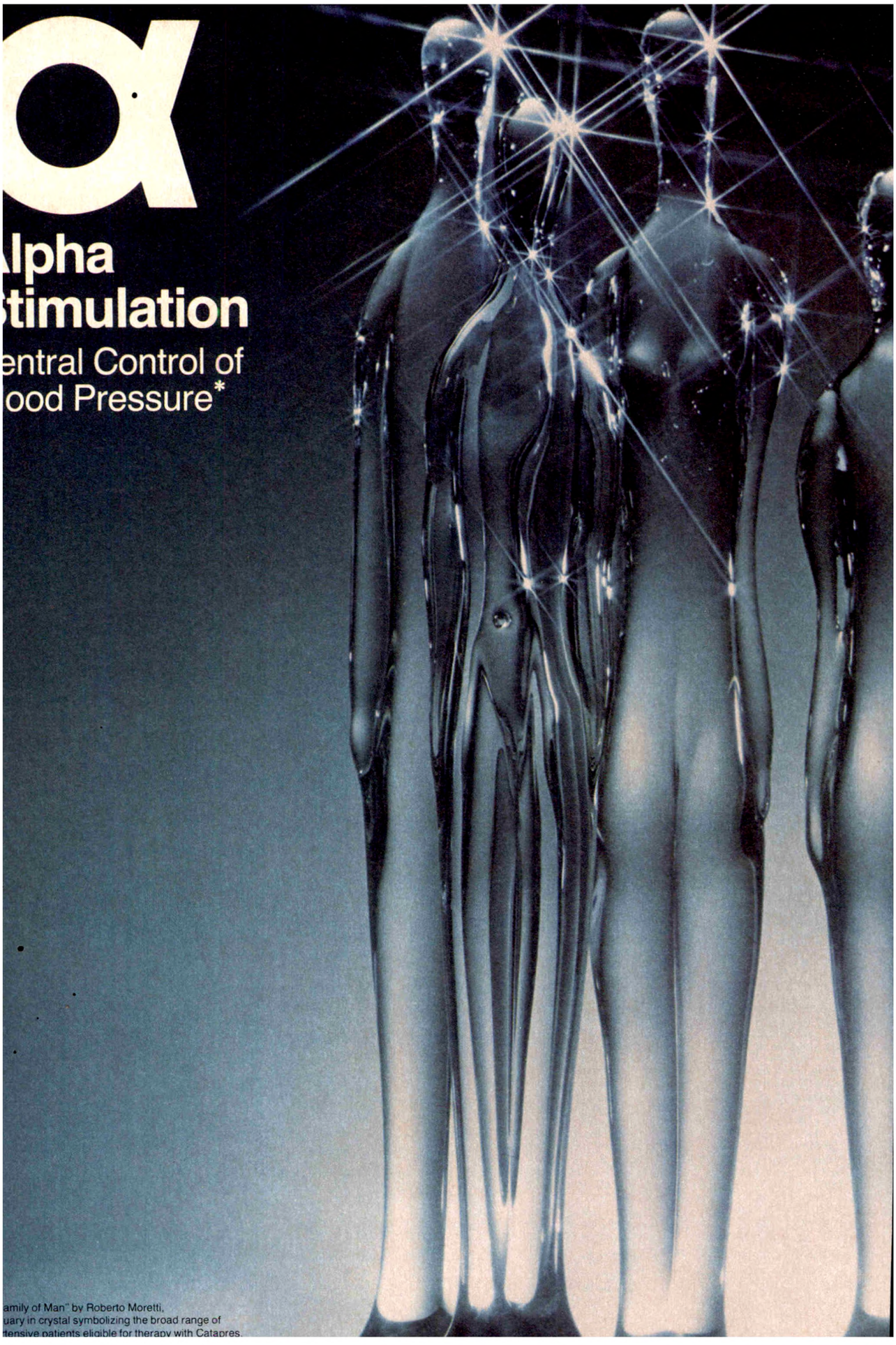
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*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

1. Data on file at Boehringer Ingelheim Ltd.

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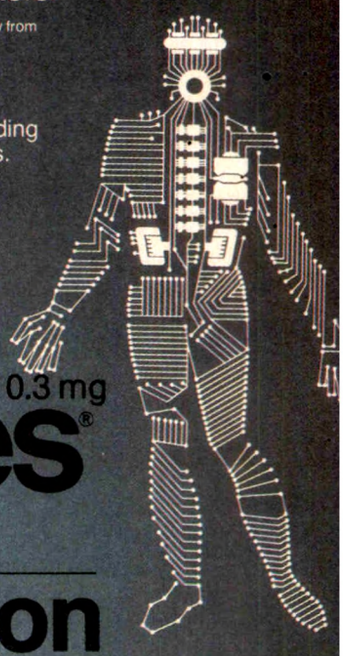

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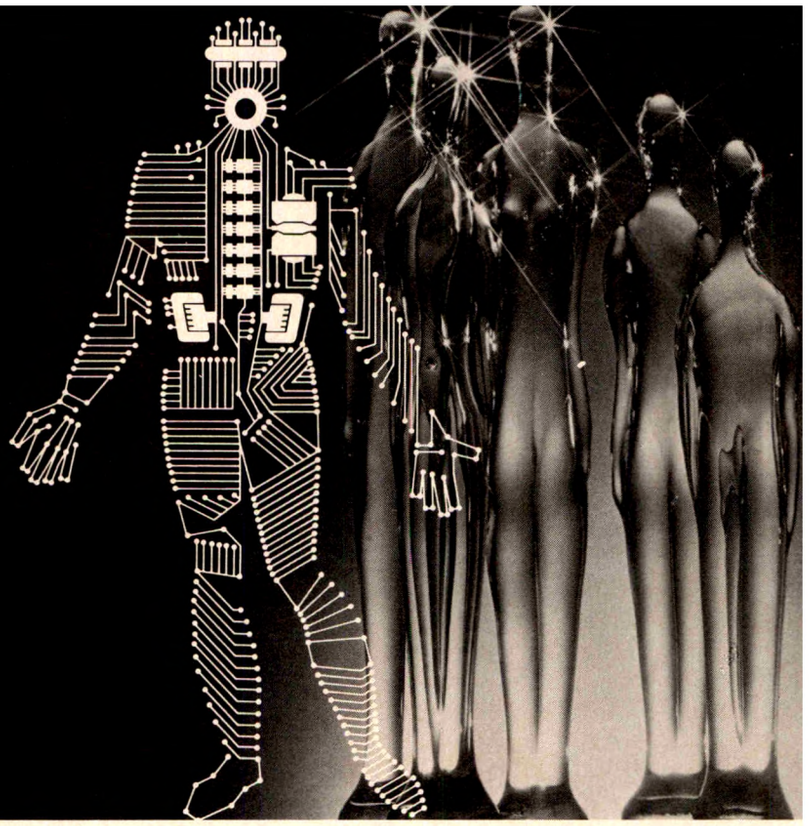

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Most common side effects are dry mouth, drowsiness, and sedation which generally tend to diminish with time.

The usual starting dose of Catapres is 0.1 mg at breal fast and 0.1 mg at bedtime. Some patients may benef from a starting dose of 0.1 mg at bedtime.

Usual daily dose range—0.2—0.8 mg

Maximum daily dose—2.4 mg
Doses as high as this have rarely been employed.

For optimal results, the dose of Catapres must be adjusted according to the patient's individual blood pressure response.

Catapres®
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Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 mont longer.

Adverse Reactions: The most common reactions are dry mouth, drowsines sedation. Constipation, dizziness, headache, and fatigue have been repo Generally these effects tend to diminish with continued therapy. The follo reactions have been associated with the drug, some of them rarely. (In s instances an exact causal relationship has not been established.) These inc Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalit liver function tests; one report of possible drug-induced hepatitis without ic and hyperbilirubinemia in a patient receiving clonidine hydrochloride, c thalidone and papaverine hydrochloride. Weight gain, transient elevation of l glucose, or serum creatine phosphokinase: congestive heart failure, Rayn phenomenon; vivid dreams or nightmares, insomnia, other behavioral cha nervousness, restlessness, anxiety and mental depression. Also rash gioneurotic edema, hives, urticaria, thinning of the hair, pruritus not assoc with a rash, impotence, urinary retention, increased sensitivity to alcohol, dry itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecom weakly positive Coombs' test, asymptomatic electrocardiographic abnorma manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished c sent reflexes and vomiting followed the accidental ingestion of Catapres (clon hydrochloride) by several children from 19 months to 5 years of age. G lavage and administration of an analeptic and vasopressor led to complet covery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-m intervals usually abolishes all effects of Catapres, (clonidine hydrochloride) dosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0. (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000. available as 0.3 mg (peach) oval, single-scored tablets in bottles of 100.

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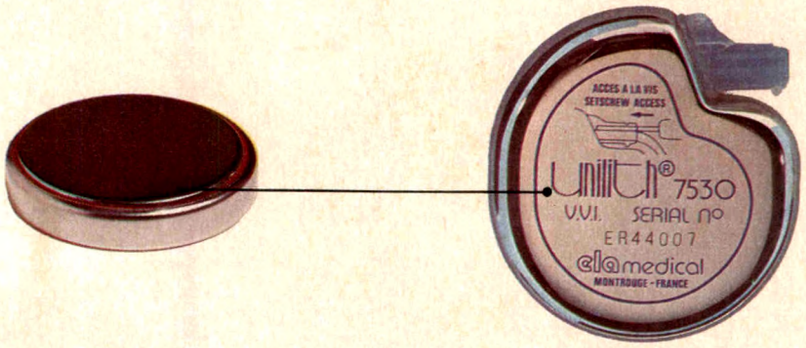

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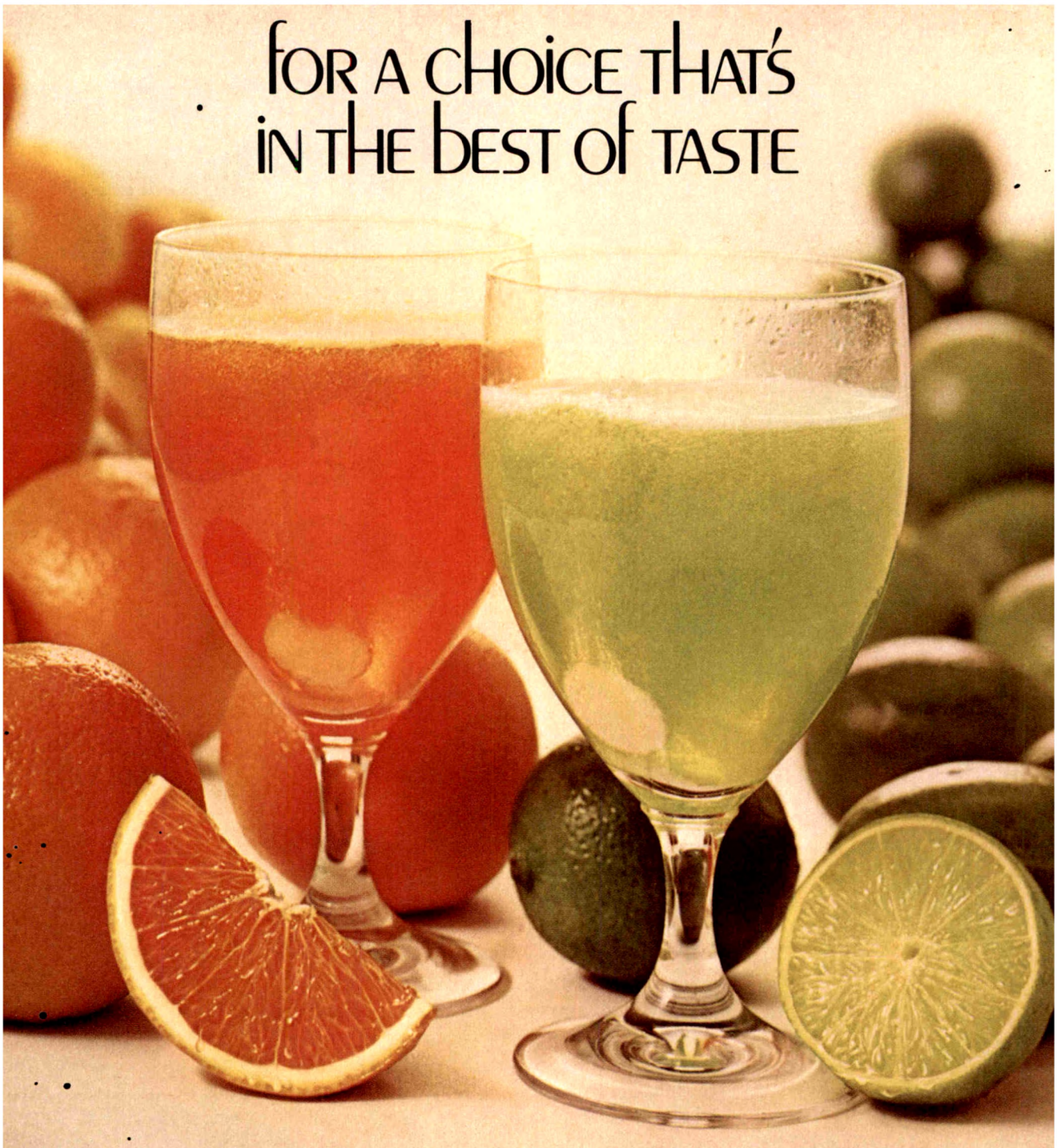

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Marquette Breaks The Cost Barrier In Computer ECG Processing

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To determine the optimal noninvasive method for the demonstration o endocarditic vegetations, 35 consecutive episodes of clinically diagnosec endocarditis in 33 patients were studied with M mode and two dimensiona echocardiography, and with gallium-67 citrate and technetium-99m stannous pyrophosphate cardiac scanning. Clinical criteria for the diag nosis of endocarditis were: temperature higher than 38° C; sustainec bacteremia with at least three positive blood cultures; no extracardiac focus of bacteremia; and known underlying heart disease, a new o changing murmur or a history of intravenous drug abuse with radiologic evidence of septic pulmonary emboli. M mode echocardiography detectec 18 vegetations in 17 of the 35 episodes of endocarditis studied (49 percen positive); two dimensional echocardiography detected 30 vegetations in 28 of the 35 episodes studied (80 percent positive). In contrast, nc vegetations were detected with technetium-99m stannous pyrophosphate scanning, and only two gallium-67 citrate scans were positive. The ad vantage of the two dimensional echocardiographic technique over al others tested was particularly notable for the identification of aortic and tricuspid valve vegetations.

The clinical diagnosis of endocarditis may now be confirmed by noninvasive methods that visualize endocardial vegetations. Several new techniques are currently being used for this purpose with varying results. M mode echocardiography has been employed in the detection of valve vegetations since the first reports of its usefulness in 1973.[1,2] The published sensitivity of this method ranged from 34 to 55 percent in series that included both right- and left-sided endocarditis.[3,4] Two dimensional echocardiography may be a more useful means of identifying vegetations since it provides a cross-sectional view of the cardiac structures, thus allowing more of the valve surfaces to be visualized. There are, however, conflicting reported data regarding the relative sensitivities of the M mode and two dimensional echocardiogram in detecting valve vegetations. Several reports[5,6] have shown the two dimensional to be superior to the M mode technique, whereas others[7,8] have indicated no difference between the two in their ability to detect vegetations.

Two recent studies of patients and animals with endocarditis have suggested that radionuclide imaging may prove to be an additional means of identifying valve vegetations. In one series, 7 of 11 patients with clinical endocarditis had a positive gallium-67 citrate cardiac scan, although the specific heart valve was not identifiable.[9] Technetium-99m stannous pyrophosphate scanning has shown abnormal accumulation of the isotope in experimentally induced Streptococcus sanguis endocarditis of the rabbit aortic valve.[10]

In this study, we attempted to determine the comparative usefulness of M mode echocardiography, two dimensional echocardiography, gallium-67 citrate scanning and technetium-99m stannous pyrophosphate imaging in the detection of valve vegetations in patients with infective endocarditis.

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Methods

Patient Selection

From July 1978 through June 1979 78 consecutive patients admitted to Beth Israel Medical Center underwent evaluation for suspected infective endocarditis. A clinical diagnosis of infective endocarditis was based on the following strict criteria: temperature higher than 38° C; sustained bacteremia with at least three positive blood cultures; no other documented source of infection; and known underlying valve disease, a new or changing heart murmur or a history of intravenous drug abuse with radiologic evidence of septic pulmonary embolic phenomena.

Clinical features: Thirty-three patients with 35 episodes of endocarditis met these criteria for entry into the study. In 21 cases, right-sided endocarditis was diagnosed clinically on the basis of intravenous drug abuse and pulmonary emboli or a murmur consistent with tricuspid insufficiency (a blowing systolic murmur along the left sternal border that increased with inspiration). No attempt was made to distinguish between tricuspid and pulmonary valve endocarditis because the distinction was frequently not possible on the basis of clinical findings alone. Seven patients with holosystolic or late systolic apical murmurs that radiated to the axilla were believed to have mitral valve endocarditis. Aortic valve endocarditis was thought to be present clinically in five patients: Three patients had an aortic diastolic murmur and two had a murmur consistent with aortic stenosis. One patient with a history of intravenous drug abuse, multiple pulmonary emboli and a new aortic diastolic murmur was thought to have right-sided as well as aortic valve endocarditis. In an additional patient with a soft ejection systolic murmur along the left sternal border and paroxysmal atrial fibrillation, it was not clear which valve was involved.

Clinical data on these patients are summarized in Table 1. The patients ranged in age from 20 to 89 years (mean of 39). Six patients were women and 27 were men. Twenty-four patients had a history of intravenous drug abuse. Eight patients had a known history of cardiac valve disease before their first episode of endocarditis. No patient had clinical findings suggestive of systemic emboli; 21 had clinical findings consistent with septic pulmonary emboli. Two patients had two episodes of endocarditis during the study period. Patient 22 was successfully treated for Staphylococcus aureus endocarditis, but was subsequently discovered to have endocarditis with peptostreptococcus sp. 3 months later. Patient 33 returned with recurrent viridans streptococcal endocarditis 6 months after completion of his first course of therapy.

The infecting organisms included Staphylococcus aureus (22 patients), streptococcus viridans group (6 patients), Streptococcus bovis (4 patients), enterococcus (1 patient), Streptococcus pyogenes, Group A (1 patient) and peptostreptococcus sp. (1 patient). Correlation between the infecting organism and subsequent echocardiographic findings was attempted.

Forty-five patients did not meet strict criteria for infective endocarditis. This group included 19 women and 26 men ranging in age from 17 to 90 years (mean 48). Eleven patients had a known history of cardiac valve disease; 15 had a known history of intravenous drug abuse.

Echocardiography

M mode: All 78 patients underwent M mode followed by two dimensional echocardiographic studies during the 1st week of hospitalization. M mode echocardiographic examinations were carried out with a Unirad series 100 ultrasonascope interfaced with a Honeywell 1856-A strip chart recorder. Recordings were made in the usual manner utilizing previously described techniques.[11] Diagnostic criteria for the presence of valve vegetations included the presence of a localized mass of dense shaggy echoes creating an irregular thickening of the valve. Echoes that were linear rather than shaggy or irregular were interpreted as not being indicative of a vegetation.

Two dimensional echocardiography: This procedure was carried out with a commercially available real time phased array wide angle (80°) sector scanner (Varian Associates). Images were permanently recorded on videotape and Polaroid® photographs were made of stop action frame images. Studies were performed with the patients supine or in the left lateral decubitus position. The cardiac valves were examined by placing the transducer in three different positions (parasternal, apical, subxiphoid) and utilizing various transducer angulations. From each position, one or more tomographic sections of the heart were obtained by rotating the transducer. The transducer was initially placed in the third or fourth intercostal space to the left of the sternum to obtain a long axis and short axis view of the heart.[12] The apical four chambered view was then obtained by positioning the transducer at the point of maximal impulse and directing the ultrasonic beam toward the base of the heart in a plane parallel to the long axis of the left ventricle and perpendicular to the interventricular septum.[13] The subxiphoid view was recorded next by placing the transducer just below the xiphoid process, slightly to the right of the midline and directing the transducer superiorly toward the left supraclavicular fossa.[14] The diagnosis of a vegetation required the presence of a mobile, rapidly oscillating mass that was attached to or appeared to replace normal valve tissue. Increased valve thickness by itself was considered insufficient for the diagnosis of a vegetation.

All M mode and two dimensional echocardiograms were analyzed independently by at least two observers. In each case there was agreement about the presence or absence of vegetations.

Radionuclide Cardiac Imaging

Technetium-99m stannous pyrophosphate scan: Only those patients satisfying the clinical criteria for infective endocarditis were referred for radionuclide cardiac imaging. Thirty-one patients had technetium-99m stannous pyrophosphate studies performed; three patients refused to participate in this part of the protocol and one patient died before scanning could be done. The patients were given an intravenous injection of 15 mCi of technetium-99m stannous pyrophosphate and underwent scanning 3 to 4 hours later for evidence of focal cardiac accumulation. Images of 500,000 counts were obtained on a standard field camera with a convergent collimator in the anterior and 30° and 45° left anterior oblique projections.

Gallium-67 citrate scan: Immediately after the last pyrophosphate image was obtained, 6 to 7 mCi of gallium-67 citrate was injected intravenously in 30 patients. Initial scans were carried out at 24 hours with one to three follow-up examinations over the next 8 days after gallium injection. Twenty-eight patients returned for complete studies. Cardiac imaging was performed in the anterior and 30° and 45° left anterior oblique projections on a standard field gamma camera equipped with a high energy collimator with the camera set at 93 keV. Three hundred thousand counts were recorded per image; on some of the delayed images only 200,000 counts were obtained because of the prolonged scanning time required. In order to minimize imaging time and to ensure better patient cooperation, the most abundant gallium-67 photopeak was

TABLE 1

Clinical and Diagnostic Observations in 35 Episodes of Endocarditis (33 patients)

Case	Age (yr) & Sex	Clinical Site of Involvement	Echocardiogram		Cardiac Scans		IV Drug Use	Underlying Valvular Heart Disease	Clinical Pulmonary Emboli
			2D	M Mode	Tc	Ga			
Staphylococcus Aureus Infection									
1	23M	R	AV	0	Neg	Neg	+		+
2	28M	R	TV	0	Neg	Neg	+		+
3	28F	R	TV	0	Neg	Neg	+	History of heart murmur for 1 yr	+
4	24M	R	PV	PV	Neg	Neg	+		+
5	54M	AV	AV	AV	Neg	Neg			
6	23M	R	TV	TV	ND	ND	+		+
7	29M	R	TV	0	Neg	Neg	+		+
8	28F	R	TV	TV	Neg	Neg	+		+
9	28M	R	TV	TV	Neg	Neg	+		+
10	38M	R	0	0	ND	ND	+		+
11	22M	R	AV, TV	0	Neg	Neg	+		+
12	29F	R	TV	TV	Neg	Neg	+		+
13	35M	R	TV	TV	Neg	Neg	+	Previous endocarditis 1977; no vegetation on echocardiogram in 1977	
14*	75M	AV	AV	0	Neg	Pos			
15	20M	R	TV	0	Neg	Neg	+		+
16	36M	R	TV	TV	Neg	Neg	+		+
17	38M	R	PV	PV	Neg	Neg	+		+
18	20F	R	0	0	Neg	Neg	+		+
19	24M	R	TV	TV	Neg	Neg	+		+
20	20M	R	TV	TV	Neg	Neg	+		+
21	24F	R	TV	0	Neg	Neg	+		+
22A	32M	AV, R	AV, TV	AV, TV	Neg	ND	+		+
Peptostreptococcus sp. Infection									
22B†	32M	AV	AV	AV	Neg	Neg	+		+
Enterococcus Infection									
23	58M	R	TV	0	Neg	Pos	+		+
Streptococcus pyogenes, Group A Infection									
24	27M	R	0	0	Neg	ND	+	Previous endocarditis 1976; tricuspid vegetation on echocardiogram in 1976	
Streptococcus Bovis Infection									
25	58M	MV	MV	MV	ND	ND			
26	75F	U	AV	0	Neg	Neg			
27‡	62M	AV	0	0	ND	ND			
28	70M	MV	MV	MV	Neg	Neg		History of heart murmur	
Streptococcus mitis Infection									
29	49M	MV	0	0	Neg	Neg		Mitral prolapse	
Streptococcus sanguis Infection									
30	75M	MV	0	0	Neg	Neg			
31	49M	MV	MV	0	Neg	Neg		Mitral prolapse	
Streptococcus salivarius Infection									
32	89M	AV	0	0	Neg	Neg		Aortic stenosis	
Streptococcus mutans Infection									
33A	33M	MV	MV	MV	Neg	ND	+	Mitral prolapse	
Streptococcus MG intermedius Infection									
33B	34M	MV	MV§	MV§	Neg	Neg	+	Mitral prolapse	

* Died of gastrointestinal bleeding (no postmortem study). † Aortic valve replacement. ‡ Died (postmortem study). § Unchanged from previous echocardiographic examination.

A = first episode of endocarditis; AV = aortic valve; B = second episode of endocarditis; Ga = gallium-67; IV = intravenous; MV = mitral valve; ND = not done; Neg = negative; pos = positive; PV = pulmonary valve; R = right-sided; TV = tricuspid valve; 2D = two dimensional; U = undetermined; 0 = no vegetation.

TABLE II

Comparison of Two Dimensional Echocardiography, M Mode Echocardiography, Gallium-67 Citrate Scanning and Technetium-99m Stannous Pyrophosphate Imaging in Detecting Valve Vegetations

Diagnostic Test	Episodes Studied (n)	Positive Tests n	Positive Tests %
Two dimensional echocardiography (2D)	35	28	80
M mode echocardiography	35	17	49
Gallium-67 citrate	28	2	7
Technetium-99m stannous pyrophosphate	31	0	0
Chi-square (χ^2) test performed:			
2D vs. M mode:	$\chi^2 = 7.5$; $p < 0.01$		
2D vs. gallium:	$\chi^2 = 33$; $p < 0.001$		
M mode vs. gallium:	$\chi^2 = 13.8$; $p < 0.001$		

TABLE III

Comparison of Clinical and Echocardiographic Localization of Valve Vegetations in 35 Episodes of Endocarditis

Valve	Method of Detection: Clinical Examination	Echocardiogram: 2D	Echocardiogram: M Mode
Aortic	6	4*	3
Mitral	7	5	4
Right-sided	21	18 (16 TV; 2 PV)	11 (9 TV; 2 PV)
Undetermined	1	1(AV)	0
Total	35	28	18

* Does not include two additional aortic valve vegetations detected with two dimensional echocardiography but unsuspected clinically in two patients (Cases 1 and 11) with concomitant right-sided endocarditis.

AV = aortic valve; PV = pulmonary valve; TV = tricuspid valve.

ised with the recognition that a necessary loss of resolution night result.

All radionuclide scans were reviewed independently by at least two observers. In each case there was agreement regarding the interpretations.

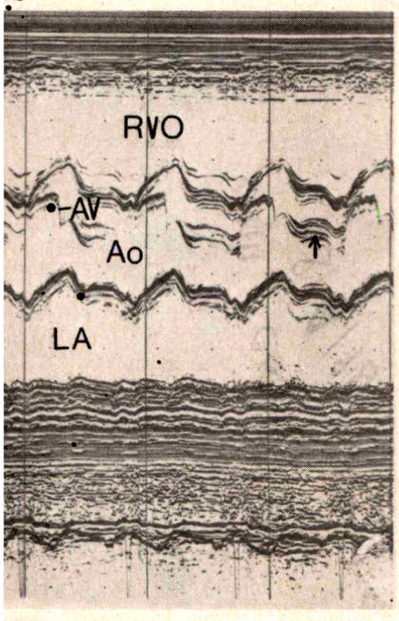
Surgical or autopsy confirmation was available in two patients. One patient died before operation; one patient had successful aortic valve replacement. An attempt was made to correlate the anatomic and echocardiographic findings in these two patients.

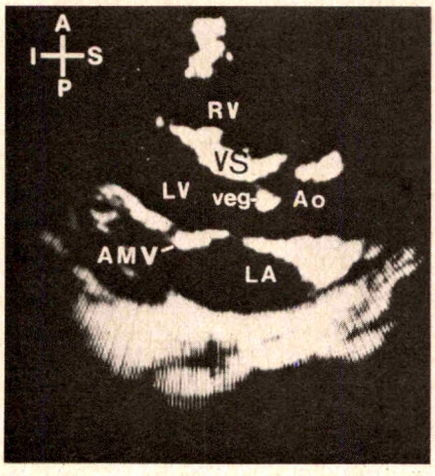
Statistical analysis was performed with the chi-square method.

Results

Echocardiograms: Among the 45 patients who did not meet the clinical criteria for endocarditis, no findings consistent with vegetative lesions were seen on either M mode or two dimensional echocardiography.

Echocardiographic findings in those patients meeting the clinical criteria for endocarditis are summarized in Table I. This group consisted of 33 patients with 35 episodes of endocarditis. Vegetations were visualized with two dimensional echocardiography in





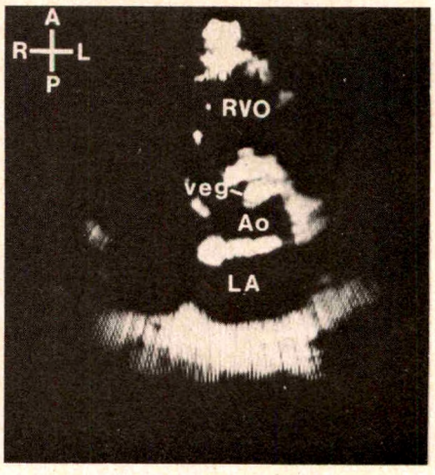


FIGURE 1 (left). Case 1. M mode echocardiogram of the aortic root (Ao). The **arrow** points to multiple linear diastolic echoes in the region of the aortic valve (AV). No definite vegetations are seen. LA = left atrium; RVO = right ventricular outflow tract.

FIGURE 2 (center and right). Same patient. Two dimensional echocardiogram showing long axis view of left heart **(center)** and short axis view at the level of the aortic root and left atrium **(right panel)**. A vegetation (veg) can be seen in the aortic root involving the left coronary cusp of the aortic valve. A = anterior; AMV = anterior leaflet of mitral valve; I = inferior; L = left; LV = left ventricle; P = posterior; R = right; RV = right ventricle; S = superior; other abbreviations as in Figure 1.

28 (80 percent) of the 35 episodes of endocarditis and with the M mode method in 17 episodes (49 percent) (Table II). A total of 30 valve vegetations were visualized in 28 patients with two dimensional echocardiography. Two patients had vegetations on both the aortic and the tricuspid valve: In one (Case 22A) involvement of both valves was suspected clinically; in the other (Case 11) only the tricuspid lesion was suspected. Patient 1 was thought clinically to have right-sided endocarditis; however, the two-dimensional echocardiogram revealed only an aortic valve vegetation and normal right-sided valves. By M mode technique, 18 valve vegetations were seen in 17 patients.

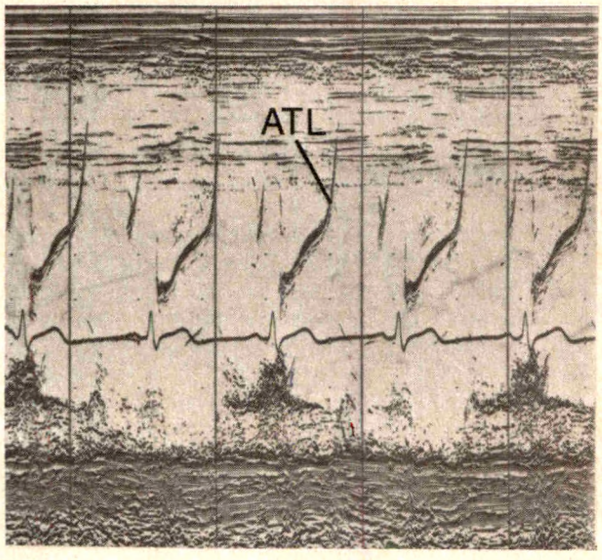
The valve distribution of vegetations suspected clinically and detected by echocardiography is summarized in Table III. The increased sensitivity of the two dimensional method was particularly evident in aortic and tricuspid vegetations. Figure 1 is an M mode echocardiogram from a patient with aortic valve endocarditis. There are a few increased linear diastolic echoes in the region of the aortic valve, but no definite vegetations are seen. Figure 2 is a two dimensional echocardiogram from this patient showing a vegetation on the left coronary cusp of the aortic valve. In Figure 3 a normal-appearing tricuspid valve is seen in the M mode echocardiogram. The two dimensional echocardiogram from this patient in Figure 4 shows a small polypoid vegetation on the anterior leaflet of the tricuspid valve.

Seven patients had no vegetations detectable with either echocardiographic method. No vegetations were detected with the M mode technique that were not demonstrated on two dimensional echocardiographic studies.

When the patients are categorized by infecting organisms, 20 of the 22 patients with Staphylococcus aureus had a positive two dimensional echocardiogram 12 of which were also positive on M mode examination. In contrast, only 8 of the 13 patients with nonstaphylococcal endocarditis had a positive two dimensional study and only 5 a positive M mode study.

Radionuclide scanning: All 31 patients studied with technetium-99m stannous pyrophosphate cardiac scanning had a negative scan. Of the 28 patients who had complete gallium-67 citrate isotope studies, two had a positive study. In the first patient (Case 23) a faint area of activity appeared between the sternum and the anterior costal margin at 24 hours and persisted at 4 and 6 days after injection of gallium. The second patient (Case 14) also had increased uptake at 24 hours in this area, which became brighter with repeated imaging on days 3 and 5 after injection of gallium. Both of these patients had two dimensional echocardiographic studies that showed valve vegetations. The results of the echocardiographic and radionuclide studies are compared in Table II.

Surgical or autopsy confirmation: Patient 27 had negative echocardiographic studies. Postmortem examination disclosed vegetations measuring 1 to 3 mm on all aortic cusps with aneurysmal dilatation and perforation of the mitral valve. Patient 22 underwent aortic valve replacement. This patient initially had Staphylococcus aureus endocarditis with vegetations on both the tricuspid and the aortic valve that had resolved on echocardiography at the completion of antibiotic therapy. The patient had clinical evidence of mild aortic insufficiency. Two months later when a second episode of endocarditis was discovered, new tricuspi



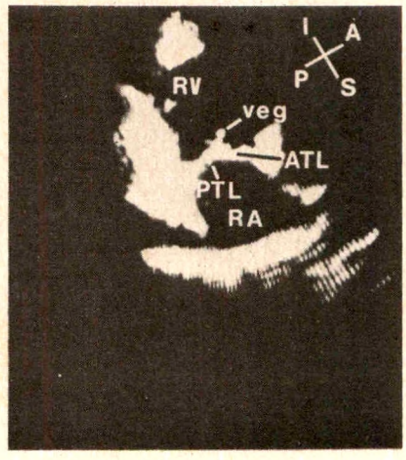


FIGURE 3 (left). Case 15. M mode echocardiogram showing normal anterior tricuspid leaflet (ATL).

FIGURE 4 (right). Same patient. Two dimensional echocardiogram showing long axis view through the right atrium (RA) and right ventricle (RV). A small vegetation (veg) is present on the ventricular side of the anterior tricuspid leaflet. PTL = posterior tricuspid leaflet; other abbreviations as before.

'egetations were seen on echocardiography; these again 'esolved during antibiotic therapy. At the time of aortic 'alve replacement the surgeon reported the tricuspid 'alve to be free of vegetations. Small vegetations were ıoted on pathologic examination of the aortic valve.

Discussion

Because the natural history and prognosis of endo-:arditis is in large part determined by the valve of ori-;in—with left-sided and particularly aortic valve dis-:ase associated with the most serious hemodynamic equelae—accurate identification of the infected heart 'alve becomes a vital component in patient manage-nent. This determination may not always be made with :ertainty on clinical grounds, especially when more than)ne valve is involved by the infectious process. Thus, a ıumber of recently developed noninvasive techniques ıave been applied for the detection of valve vegetations vith various degrees of success.

Advantages and applications of two dimensional :chocardiography: In the present study, valve vege-ations were identified by two dimensional echocardi-)graphy in 28 of 35 cases of endocarditis diagnosed linically. Whereas two dimensional echocardiography ncreased the number of vegetations detected with the tandard M mode technique in cases of aortic, mitral nd tricuspid endocarditis, its most distinct advantage 'as noted in visualization of aortic and tricuspid valve 'egetations. The finding of unsuspected aortic vegeta-ions in two patients with right-sided lesions and in one)atient in whom the involved valve could not be deter-ıined clinically proved to be a useful diagnostic aid. 'he observed increase in sensitivity with the two di-ıensional echocardiogram is related to better appre-iation of the spatial anatomy of the vegetations in elation to adjacent cardiac structures. In addition, the bility to examine the heart and its chambers from ıultiple transducer positions allows more complete isualization of valve leaflets and vegetative lesions.

The factors that account for echocardiographic vi-ualization of valve vegetations are complex. It has een established that vegetations must be greater than to 3 mm in size for M mode echocardiographic visu-lization.[15,16] In accord with these data, one of our pa-ients who had aortic valve vegetations measuring 1 to mm on postmortem examination had no vegetations etected with either two dimensional or M mode chocardiography. It has been observed in necropsy tudies[17] that tricuspid vegetations are generally larger ıan vegetations on other valves. In a series of 25 drug ddicts with endocarditis, the largest vegetations on chocardiographic evaluation were located on the tri-uspid valve.[18] The investigators postulated that the ırger anular circumference of the tricuspid valve, re-uced systolic pressure in the right ventricle and less 'equent incidence of ruptured tricuspid chordae al-)wed tricuspid vegetations to reach a larger size than ıitral valve vegetations.

There has also been some suggestion that vegetations ı patients infected with Staphylococcus aureus are ırger than vegetations in patients infected with other organisms. In a series of 65 echocardiographically evaluated patients with endocarditis, Staphylococcus aureus was noted to be more prevalent overall in the group of patients with vegetations on echocardiography, although only three of the patients in this series had tricuspid vegetations.[3] However, the investigators did not provide details of the anatomic findings. In our series it was difficult to assess the contribution of these various factors because 15 of the 18 patients with tricuspid valve vegetations on echocardiography had endocarditis due to Staphylococcus aureus.

Limitations of two dimensional echocardiography: In spite of the increased sensitivity of two dimensional echocardiography in demonstrating valve vegetations, the technique has several technical limitations. Improper use of gain settings may lead to erroneous estimation of the size of a vegetation, particularly when a phased array instrument is used. Gain settings set too high will make a vegetation appear larger than its actual size, whereas if the gain settings are set too low, image dropout may occur and the vegetation may appear smaller than it is or may be missed entirely. Furthermore, calcified or fibrotic valves and myxomatous degeneration may mimic vegetative lesions. Careful attention to technique will minimize these potential sources of error. However, there are some patients in whom a good quality echocardiogram cannot be obtained because of poor penetration of the ultrasonic beam due to interposed lung tissue or anatomic variation of the chest wall.

Technetium-99m pyrophosphate imaging in endocarditis: Cardiac scans with technetium-99m stannous pyrophosphate were negative in 31 of our patients with endocarditis who were so studied. These results were unexpected because technetium-99m stannous pyrophosphate scans in rabbits with infective and nonbacterial thrombotic endocarditis show focal uptake in the area surrounding the aortic valve vegetations and in the aortic outflow tract.[10] This radiopharmaceutical has been used successfully in both patients and animals to identify areas of acute myocardial infarction. The mechanism of its accumulation in recently necrotic myocardial tissue is still under investigation. It is known that both technetium-99m stannous pyrophosphate and calcium localize in mitochondria of acutely necrotic myocardium in animals with both acute myocardial infarction and necrosis secondary to endocarditis.[19] There is some recent evidence that technetium-99m stannous pyrophosphate also complexes with denatured protein macromolecules in these infarcted cells.[20]

There are several possible differences between patients with endocarditis and the animal model for this disease, which may explain the marked discrepancies between technetium-99m stannous pyrophosphate uptake in the animal study and in our series of patients with endocarditis. In the animal model there is probably more extensive necrosis of perivalvular and subendocardial tissue than occurs in patients with endocarditis. This would account for part of the perivalvular uptake on scanning in animals with endocarditis. The more acute the necrotic process, the more likely techne-

tium-99m stannous pyrophosphate is to accumulate in the damaged cell, as is seen in patients with myocardial infarction. Although our series included patients with both acute and subacute endocarditis, the duration of insult to adjacent myocardial cells is difficult to ascertain. Furthermore, the lesions in human endocarditis may be too small when compared with the animal model, and technically beyond the resolution of the collimator. Lastly, the experimentally induced vegetation may in fact not be comparable to the lesion of human acute endocarditis. In the animal study, uptake was similar in nonbacterial thrombotic endocarditis and infected lesions. While an initial valve platelet-fibrin thrombus is essential for the development of endocarditis in the animal model, there has been no histologic documentation that such lesions precede acute endocarditis in human beings.

Gallium-67 citrate imaging in endocarditis: In the present series, of 28 gallium-67 citrate scans performed, only 2 showed cardiac uptake, and neither positive study identified the involved heart valve. One patient had a subacute course with enterococcal endocarditis, and the other patient had acute endocarditis with Staphylococcus aureus. Their clinical courses did not differ from those of the remaining patients with a negative scan. In both patients valve vegetations were detected only with two dimensional echocardiography.

These findings are in contrast to six diffusely positive cardiac gallium scans in another series of 11 patients with endocarditis.[9] All but one of the patients had left-sided endocarditis and four of the six patients with a positive scan were infected with Staphylococcus aureus. These scans became positive between 3 and 8 days after isotope injection, whereas in our two patients with a positive gallium study the scan showed abnormal uptake at 24 hours and remained positive.

Some gallium uptake might be expected in all patients with endocarditis, because necropsy studies show myocardial inflammation in up to 60 percent or more of patients with endocarditis.[21] This is most prominent in left-sided and possibly in subacute disease.[17,22,23] Gallium presumably localizes in infected tissue by binding to polymorphonuclear leukocytes, which then accumulate in areas of acute infection. In addition, accumulation of gallium may occur as a result of increased vascularity in infected sites, tissue deposition of gallium-transferrin complexes and binding of gallium to microorganisms.[24]

There are several possible explanations to account for the discrepancies between our series and the previously cited gallium scanning study.[9] Right-sided endocarditis predominated in our series of patients. The anulus and surrounding myocardium are known to have markedly less involvement in tricuspid endocarditis than in left sided diseases.[17] Less gallium uptake might be anticipated on this basis. In addition, early antibiotic therapy has been shown to decrease leukocyte migration to infected tissue.[25] In all of our patients treatment had been initiated before gallium scanning was carried out. Furthermore, the majority of our patients probably had a more acute inflammatory process than those in the previously cited study in which five of the six patients underwent imaging at least 18 days after the onset of their symptoms. Lastly, because of the uncooperative attitude of many of our patients, an attempt was made to shorten the study time by using the more abundant lower photopeak of gallium. The resolution loss may have made subtle abnormalities undetectable. In the study by Wiseman et al.[9], 100,000–200,000 counts required 30 minutes imaging time, which we considered to be beyond the tolerance of the majority of our patients.

In our series of patients with endocarditis, technetium-99m stannous pyrophosphate and gallium scans had extremely low sensitivity in identifying valvular vegetations. A recent case report of focal accumulation of gallium-67 citrate in the left ventricle of a patient with surgically confirmed myocardial abscess suggests that scanning might find application in the demonstration of suppurative complications of endocarditis.[26] Echocardiography, and most notably the two dimensional technique, remains the only sensitive method for detecting valve vegetations in patients with endocarditis.

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Pulsed Doppler Echocardiographic Detection of Right-Sided Valve Regurgitation

Experimental Results and Clinical Significance

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Pulsed Doppler echocardiography may allow noninvasive detection of tricuspid insufficiency as disturbed or turbulent systolic flow in the right atrium and pulmonary insufficiency as turbulent diastolic flow in the right ventricular outflow tract. Accordingly, six open chest mongrel dogs were examined with Doppler echocardiography before and after surgical creation of tricuspid and pulmonary insufficiency. The Doppler technique detected the appropriate lesion in all instances, with a specificity of 100 percent.

In 121 patients (20 without heart disease, 101 with heart disease of various causes), pulsed Doppler echocardiography was used to detect right-sided valve regurgitation. Results were compared with right-sided pressure measurements and M mode echocardiographic findings in all, and with right ventricular angiography in 21 patients. Pulsed Doppler study detected tricuspid insufficiency in 61 of 100 patients, 12 (20 percent) of whom had clinical evidence of this lesion. Angiographic evidence of tricuspid regurgitation was present in 18 patients, 17 of whom had positive Doppler findings (sensitivity 94 percent), and absent in 3, all with negative Doppler findings. Pulmonary insufficiency was found on pulsed Doppler study in 47 of 91 patients, 3 of whom (all after pulmonary valvotomy) had clinical evidence of this lesion. Increased right ventricular systolic pressure (greater than 35 mm Hg) was noted more often in patients with (55 of 61 or 90 percent) than in those without (22 of 59 or 37 percent) tricuspid insufficiency ($p < 0.01$). Pulmonary arterial mean pressure was elevated (22 mm Hg or less) more often in patients with (38 of 43 or 88 percent) than in those without (24 of 64 or 38 percent) pulmonary insufficiency ($p < 0.01$).

Thus, pulsed Doppler echocardiography appears to be an accurate noninvasive technique for detection of right-sided valve regurgitation. The absence of diagnostic physical findings in many of the patients indicates that the hemodynamic severity of the Doppler-detected valve insufficiency was probably insignificant. However, because of its high incidence rate (87 percent) and association with pulmonary hypertension (87 percent), pulsed Doppler detection of tricuspid or pulmonary insufficiency, or both (in the absence of pulmonary stenosis) was found superior to M mode echocardiographic measurements (right ventricular size, pulmonary valve motion) in the prediction of pulmonary hypertension.

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The clinical detection of right-sided valve regurgitation of either tricuspid or pulmonary origin may often be difficult.[1–3] Tricuspid insufficiency may occur as a functional result of right ventricular pressure or volume overload or may be caused by infective endocarditis, congenital malformations, trauma and, infrequently, carcinoid disease.[2,4] Pulmonary insufficiency, as an isolated lesion, has been shown to be well tolerated and seldom leads to right ventricular failure. When symptoms occur, pulmonary hypertension or additional disease must be suspected.[5–10] Thus detection of right-sided valve regurgitation may assume clinical importance as a marker of a more serious underlying disease process, particularly in patients with coexistent left-sided heart disease.

Invasive procedures such as angiography have certain mitations in the identification of right-sided valve sufficiency but are probably reliable to establish the)sence of valve regurgitation.[10–12] Intracardiac pho-)cardiography may be superior to angiography in the :tection of pulmonary insufficiency.[12] Although)ninvasive techniques such as M mode echocardiog-.phy and phonocardiography are relatively insensitive dicators of right-sided valve insufficiency, echocar-ography can provide useful information on right ntricular size, abnormalities of ventricular septal otion due to right ventricular volume overload and)normalities of pulmonary valve motion that may ggest the presence of pulmonary hypertension. An curate noninvasive technique to detect right-sided lve regurgitation could therefore be of considerable inical value when results of cardiac catheterization or)ninvasive tests are not entirely diagnostic.

Pulsed Doppler echocardiography is a new noninva-ve technique that allows qualitative assessment of ood flow patterns within intracardiac chambers and us may be useful in detecting the presence of valve sufficiency or stenosis as well as a variety of congenital art defects.[13–22] The presence of disturbed or turbu-nt flow in the right atrium during systole or in the right ntricular outflow tract during diastole has been pre-med to be indicative of tricuspid or pulmonary in-fficiency, respectively. In the present study we in-stigated the sensitivity and specificity of pulsed)ppler echocardiography in detecting experimentally duced right-sided valve regurgitation. In addition, we tempted to determine the clinical significance of these ndings in patients with evidence of organic heart dis-e of various causes.

Methods

chnical Description and Procedure

Pulsed Doppler echocardiograms were performed ilizing a commercially available Echo-Doppler unit dvanced Technology Laboratories, Seattle, Wash-gton) that uses repetitive pulses of sound in a mega-rtz range similar to that of traditional M mode hocardiography. Its primary advantage over contin-)us wave Doppler recording is that the Doppler shift oduced by the velocity of blood flow can be recorded localized intracardiac positions at several depths by eans of a range-gating system.

The principle of the Doppler effect has been re-)rted previously.[14] In brief, the frequency of a re-cted sound wave is altered when the reflecting target in motion. When an ultrasonic beam is directed at nturbulent or laminar blood flow, the reflected sound ves exhibit a fairly uniform shift in frequency or)oppler shift" in either a positive or negative direction pending on the direction of flow toward or away from e transducer; the magnitude of the shift is related to th the velocity of flow and the angle of incidence be-een flow and sound. In contrast, when the ultrasonic am is directed toward turbulent blood flow, the re-cted sound waves undergo a wide and random shift frequency due to the varying velocity and direction the blood cells in the turbulent area.

The instrument consists of a 3 megahertz piezoelectric transducer with a ½ inch (1.27 cm) diameter crystal focused at 5 cm that emits 1 ms ultrasonic bursts at a pulse repetition frequency of 3,500 to 10,000 bursts/s. The returned signal is divided so that a portion is processed to create a traditional M mode display for depth reference while the remainder is used to detect the Doppler shifts. A movable range-gating system electronically creates a 2 by 4 mm teardrop-shaped area for discrete sampling of Doppler shifts at any depth selected from 2 to 15 cm along the ultrasonic beam. The Doppler effect is displayed using both an audio system and a graphic system referred to as a time interval histogram. Interpretation of the audio signal is based on its tonal quality; nonturbulent blood flow has a narrow band width pattern producing a rather musical sound, whereas turbulent flow tends to have a wide band width pattern, producing a harsh, scratchy sound. The time interval histogram interprets frequency shifts of the reflected ultrasound utilizing a zero-crossing technique previously described.[15] The graphic display consists of a series of dots printed above (positive shift) or below (negative shift) a baseline, the distance away from baseline reflecting the magnitude of the shift. The conventional display contains the M mode echocardiogram with a superimposed line indicating location of the sample volume, an electrocardiogram and the time interval histogram (Fig. 1).

Clinical Studies

Tricuspid insufficiency: *The technique employed in the clinical studies was as follows (Fig. 1):* The 3.0 megahertz transducer was placed along the left sternal border in a manner similar to that used for standard M mode echocardiography and directed medially to record the tricuspid valve. The sample volume was then placed in the right atrium slightly posterior to the systolic motion of the tricuspid valve echo and anterior to the atrial septum. After the instrument gain was set to an optimal signal to noise ratio, systolic turbulence was sought by moving the sample volume within the space posterior to the tricuspid valve (right atrium) while carefully listening for turbulent sounds from the speakers. However, regardless of the audio signals, the diagnosis of tricuspid insufficiency depended on the objective interpretation of the time interval histogram for the presence of systolic turbulence in the right atrium. Threshold levels in the instrument were set to the maximal possible level that allowed adequate signal recording with minimal baseline noise. On the basis of our previous experience with left-side valve regurgitation[22] and with aortic stenosis,[16] we defined turbulence on the time interval histogram as a frequency dispersion greater than 1 cm in amplitude. The amplitude and duration of turbulence were measured (Fig. 1). The duration of turbulence was expressed as a fraction of the duration of systole.

Pulmonary insufficiency (Fig. 2): The presence or absence of pulmonary insufficiency was assessed by directing the transducer superiorly and leftward from the aortic root to record the pulmonary valve. The sample volume was then placed in the echo-free space

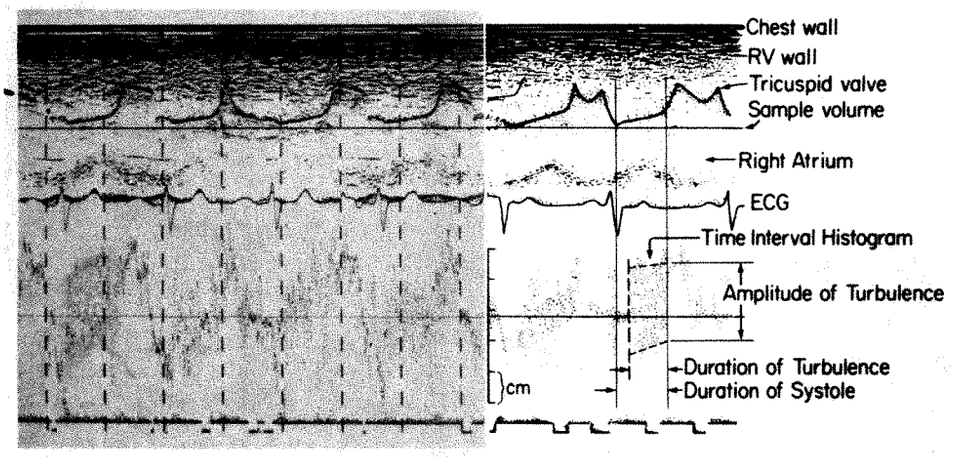

FIGURE 1. Pulsed Doppler echocar diographic examination in a patient wit tricuspid insufficiency. **Top half,** mode echocardiogram indicating lo cation of the sample volume posteric to the tricuspid valve in the right atrium **Bottom half,** time interval histogram Note the wide dispersion of **dots** abov and below a zero frequency shi baseline during systole, indicatin systolic turbulence in the right atrium The amplitude and duration of turbu lence and the duration of systole ar outlined by **interrupted lines** in the d agram on the **right.** The positive un form frequency shifts during diastol are produced by the normal diastoli inflow across the tricuspid valve. EC = electrocardiogram; RV = right ver tricle.

anterior to the pulmonary valve echo representing the right ventricular outflow tract. Care was taken not to place the sample volume through the pulmonary valve orifice or distal to the valve in the pulmonary artery. Whenever the pulmonary valve echo could not be well visualized, the transducer was directed toward the pulmonary valve area, gradually moving the sample volume until the characteristic opening and closing clicks of the valve were heard. The sample volume was then moved anteriorly into the right ventricular outflow tract. Diastolic turbulence was sought while the sample volume was moved within the right ventricular outflow and by carefully listening for turbulent sound from the speakers. However, the diagnosis of pulmonary insufficiency depended on the objective interpretation of the time interval histogram for the presence of a wide (greater than 1 cm) frequency dispersion. The amplitude in absolute centimeters and the duration of the diastolic turbulence (expressed as a fraction of diastole) were measured as shown in Figure 2.

All patients underwent a complete pulsed Doppler examination including the left side of the heart for the presence of mitral or aortic regurgitation as well as aortic stenosis utilizing standard techniques previously reported from this laboratory.[16,22] Interpretation of the time interval histogram for evidence of tricuspid or pulmonary insufficiency was performed by two separat observers without knowledge of the clinical, angio graphic or hemodynamic data available on each pa tient.

Study patients: A total of 121 patients were studie with both M mode and pulsed Doppler echocardiogra phy. Twenty patients (12 men and 8 women with a mea age 41 years [range 25 to 62]) without clinical, electro cardiographic or M mode echocardiographic evidenc of organic heart disease served as normal contro subjects. One hundred one patients (50 male and 5 female with a mean age 44 years [range 2 to 83]) wit evidence of heart disease of various causes (Table I were selected in a consecutive manner on the basis o two criteria: (1) the indications for diagnostic right and left heart catheterization, and (2) the diagnostic quality of a standard M mode echocardiogram. Valvular hear disease was present in 60 percent of the patients an congenital heart disease was the second most commo abnormality (25 percent). Pulsed Doppler studies wer technically inadequate for detection of tricuspid o pulmonary insufficiency in 1 and 10 patients, respec tively.

All 101 patients underwent diagnostic right and lef heart catheterization utilizing standard techniques Right ventricular angiography was performed in the 20

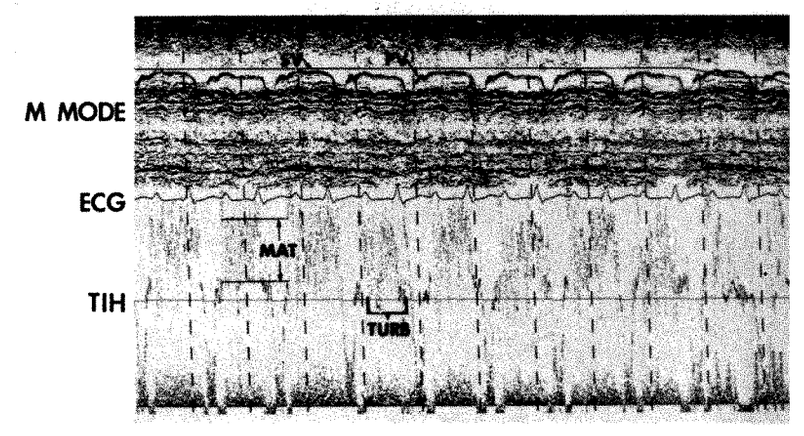

FIGURE 2. Pulsed Doppler echocardiographic examination in a patient with pulmonary insufficiency. The sample volume (SV) is located anterior to the pulmonary valve (PV) in the right ventricular outflow tract. Note the negative smooth flow-velocity curve in the time interval histogram (TIH) during systole produced by the blood flowing away from the sound waves, and the wide frequency dispersion (indicating turbulence) that extends through most of diastole. In the **far right** portion of the figure (the last two cardiac cycles), the sample volume is repositioned within the pulmonary valve and diastolic turbulence (TURB) is no longer demonstrated in the time interval histogram. ECG = electrocardiogram; MAT = maximal amplitude turbulence.

TABLE I

Summary of Data on 101 Patients With Heart Disease

Cause	Total	Incidence of PH (%)	Incidence of TI		Incidence of PI	
			n	%	n	%
Rheumatic*	48	94	35/47	74	26/45	58
Congenital	22	32	11/22	50	9/20	45
ASD	5	60				
VSD	3	0				
PS†	9	0				
TA	1	100				
APVR	1	0				
Eisenmenger's complex	3	100				
Primary PH	1	100	1/1	100	0/1	0
AVD (nonrheumatic)	7	57	3/7	43	2/7	29
MVD (nonrheumatic)	3	67	1/3	33	2/3	67
Cardiomyopathy	9	67	5/9	56	6/9	67
Congestive	6	67				
Hypertrophic	3	67				
Endocarditis	3	67	3/3	100	2/3	67
Trauma	1	0	0/1	0		0
CAD	6	33	1/6	17	0/2	0
Chronic AF	1	0	1/1	100	0/1	0

* All patients had mitral valve disease. †Includes three patients with pulmonary valvotomy.
AF = atrial fibrillation (idiopathic); APVR = anomalous pulmonary venous return; ASD = atrial septal defect; AVD = aortic valve disease; CAD = coronary artery disease; MVD = mitral valve disease; PH = pulmonary hypertension; PI = pulmonary insufficiency; PS = pulmonary stenosis; TA = tricuspid atresia; TI = tricuspid insufficiency; VSD = ventricular septal defect.

right anterior oblique projection in 21 patients with injection of 40 to 50 cc of Renografin® 76 through a side hole angiographic catheter at a rate of 10 cc/s. Ventricular ectopic beats were excluded from evaluation.

Experimental Studies

Six open chest mongrel dogs were examined with M mode and pulsed Doppler echocardiography by manually placing the transducer on the anterior surface of the heart and directing the sound waves into the tricuspid valve with the right atrium behind it or into the right ventricular outflow tract and pulmonary valve. Experimental right-sided valve regurgitation was accomplished by suturing one or more leaflets of the particular valve to the valve ring. In each animal, 10 cc of normal saline solution was injected rapidly through a flow-directed catheter inserted into the right ventricle or pulmonary artery through the left jugular vein in order to create microcavitations that could be recorded on the M mode echocardiogram. Thus we could establish the presence of valve regurgitation by the appearance of microcavitations in the right atrium during systole (indicating tricuspid insufficiency) or in the right ventricular outflow tract in diastole (indicating pulmonary insufficiency). The pulsed Doppler examinations were performed in a manner analogous to the clinical studies. At the completion of the study, the animals were killed and the hearts examined to ensure proper placement of the sutures and disruption of valve competency.

Statistical analysis: Statistical evaluation was carried out by chi-square analysis; significance was established at a level of $p < 0.05$.

Results

Experimental Studies

None of the six dogs had evidence of tricuspid or pulmonary insufficiency by microcavitations or by pulsed Doppler echocardiography before surgical valve disruption or with placement of the catheter through the valve orifices. Microcavitations were observed in the right atrium during systole or in the right ventricular outflow tract during diastole in each animal with surgical induction of tricuspid or pulmonary insufficiency, respectively (Fig. 3 A and C). In each instance, the pulsed Doppler recording was also diagnostic of tricuspid or pulmonary insufficiency (Fig. 3 B and D). Thus the sensitivity of pulsed Doppler echocardiography in detecting experimental tricuspid pulmonary insufficiency was 100 percent. The specificity of the technique was also 100 percent.

Clinical Studies

None of the 20 patients without clinical evidence of heart disease had Doppler evidence of systolic turbulent flow in the right atrium or diastolic turbulent flow in the right ventricular outflow tract. Table I lists the diagnoses and the incidence of flow disturbances in the 101 patients with heart disease. Flow disturbances compatible with tricuspid or pulmonary insufficiency, or both, were frequently found on Doppler recording in patients with rheumatic heart disease, congenital heart disease and cardiomyopathy. In total, Doppler evidence of tricuspid insufficiency was found in 61 of 100 patients and pulmonary insufficiency in 47 of 91 patients with adequate studies. Thirty-one patients had evidence of both lesions.

Tricuspid insufficiency: A systolic murmur compatible with tricuspid insufficiency was audible in 12 of 61 patients (20 percent) with Doppler evidence of tricuspid regurgitation and in none of the 39 patients without tricuspid insufficiency on Doppler recording. Comparison of Doppler findings with right ventriculography in 21 patients revealed angiographic evidence of tricuspid regurgitation in all 17 patients with a positive Doppler study and absence of this lesion in 3 of 4

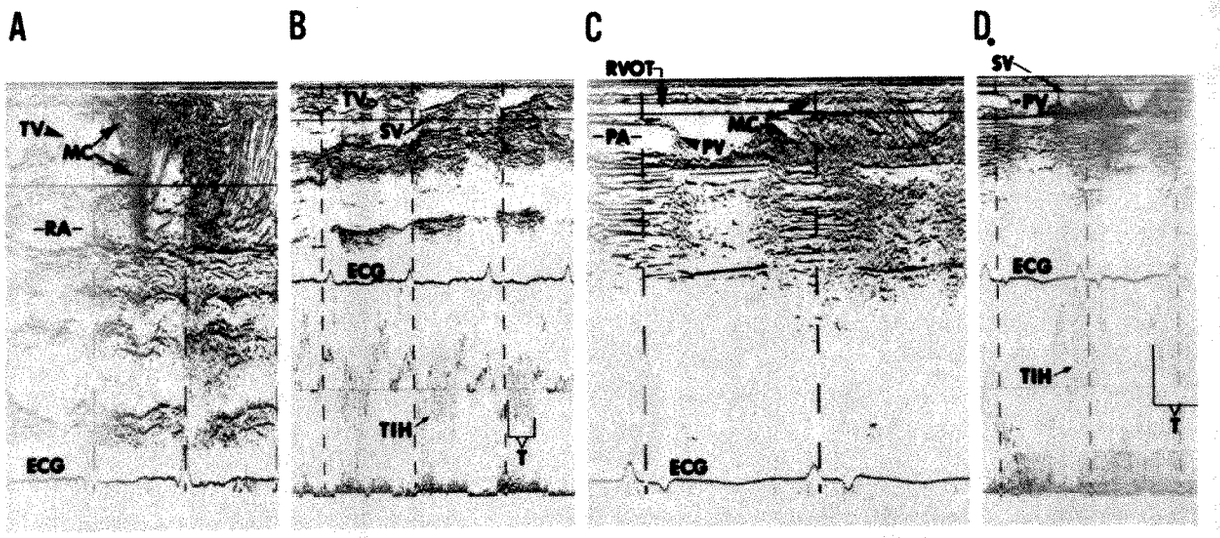

FIGURE 3. A, M mode echocardiogram of the regurgitant tricuspid valve (TV) in an open chest dog. After rapid injection of saline solution into th right ventricle, microcavitations (MC) appear initially in the right ventricular inflow tract and subsequently in the right atrium (RA), a finding consister with tricuspid insufficiency. **B,** pulsed Doppler echocardiogram from the same animal demonstrating systolic turbulence (T) in the time interv histogram (TIH) with the sample volume (SV) placed beneath the tricuspid valve in the right atrium. **C,** M mode echocardiogram of the regurgitar pulmonary valve (PV) demonstrating the injection of saline solution into the pulmonary artery (PA) and rapid visualization of microcavitations i the right ventricular outflow tract (RVOT) during diastole, a finding diagnostic of pulmonary insufficiency. **D,** pulsed Doppler echocardiogram fro the same animal demonstrating diastolic turbulence in the time interval histogram with the sample volume located in the right ventricular outflo tract. ECG = electrocardiogram.

patients with a negative Doppler study; the sensitivity of pulsed Doppler echocardiography against angiography was therefore 94 percent.

The relation of Doppler evidence of tricuspid regurgitation to the presence of right ventricular pressure overload is shown in Table II. Chi-square analysis revealed a significant ($p < 0.01$) association between the two abnormalities; 90 percent of patients with versus 37 percent of those without tricuspid insufficiency on Doppler study had a systolic right ventricular pressure greater than 35 mm Hg. Furthermore, the incidence of systolic turbulence in the right atrium compatible with tricuspid insufficiency in patients with and without increased right ventricular pressure was 71 and 14 percent, respectively.

Pulmonary insufficiency: A basal diastolic low pitched murmur was audible in the three patients with previous pulmonary valvotomy; all three also had evidence on Doppler recording of disturbed or turbulent diastolic flow in the right ventricular outflow tract. A basal diastolic high pitched murmur was audible in 35 patients, 20 with and 15 without diastolic turbulence in the right ventricular outflow; all 35 patients had evidence of aortic insufficiency on Doppler study (35 patients) or angiography (33 patients).

A significant association was observed between Doppler evidence of pulmonary insufficiency and pulmonary hypertension (Table III); 86 percent of the patients (excluding the three patients with previous valvotomy) with versus 38 percent of those without diastolic turbulence in the right ventricular outflow tract had a mean pulmonary arterial pressure greater than 22 mm Hg ($p < 0.01$). Furthermore, the incidence of diastolic turbulence in the right ventricular outflow tract in patients with and without pulmonary hypertension was 61 and 13 percent, respectively. Doppler evidence of pulmonary insufficiency with normal pulmonary pressure was present in six patients: two with a left to right shunt at the atrial level, two with cardiomyopathy, one with mitral stenosis and one with pulmonary valve stenosis.

A significant relation was observed between the duration of diastolic turbulence in the right ventricular outflow tract, expressed as a fraction of diastole, and the severity of pulmonary hypertension (Fig. 4). Mean pulmonary arterial pressure was 40 mm Hg or greater in 83 percent of the patients with diastolic turbulence persisting for more than two thirds of diastole, in 3 percent of patients with turbulence lasting for one third to two thirds of diastole and in none of the patients with turbulence lasting one third or less of diastole ($p < 0.001$).

TABLE II

Tricuspid Insufficiency on Doppler Echocardiography: Relation to Right Ventricular Hypertension

	Patients With TI (n = 61)		Patients Without T (n = 59*)	
	n	%	n	%
RVP >35 mm Hg (n = 77)	55	90	22	37
RVP <35 mm Hg (n = 43)	6	10	37	63
			$p < 0.01$ (chi-square analysis)	

* Includes the 20 patients without heart disease.
RVP = right ventricular systolic pressure; TI = tricuspid insuf ciency.

TABLE III

Pulmonary Insufficiency on Doppler Echocardiography: Relation to Pulmonary Hypertension

	Patients With PI* (n = 44)		Patients Without PI (n = 64†)	
	n	%	n	%
Mean PAP >22 mm Hg (n = 62)	38	86	24	38
Mean PAP <22 mm Hg (n = 46)	6	14	40	62
		p <0.01		

* Excludes three patients with pulmonary valvotomy. † Includes 20 patients without heart disease.
PAP = pulmonary arterial pressure; PI = pulmonary insufficiency.

Pulsed Doppler versus M mode echocardiographic prediction of pulmonary hypertension: The sensitivity and predictive values of the pulsed Doppler and the M mode echocardiographic findings for pulmonary hypertension are listed in Table IV. In the absence of pulmonary stenosis, pulsed Doppler evidence of tricuspid or pulmonary insufficiency, or both, had a sensitivity of 87 percent and a predictive value of 87 percent for pulmonary hypertension. The occurrence of both Doppler abnormalities together had a sensitivity of 41 percent and a predictive value of 90 percent. In contrast, M mode echocardiographic evidence of right ventricular enlargement (greater than 2.8 cm, left lateral recumbent position) occurred in only 31 percent of patients with pulmonary hypertension; the predictive value of this finding was 93 percent. A reduced amplitude (less than 2 mm) of the pulmonary valve *a* wave had a sensitivity and predictive value comparable with those of the pulsed Doppler finding of tricuspid or pulmonary insufficiency, or both. However, analysis of the pulmonary valve echo for this abnormality was possible in only 31 of 92 patients with heart disease.

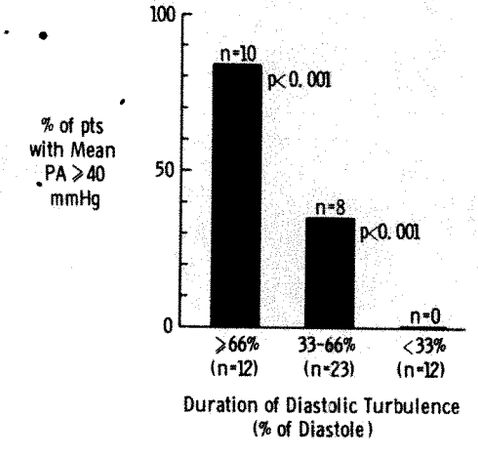

FIGURE 4. Incidence of mean pulmonary arterial pressures (PA) greater than 40 mm Hg in patients (pts) with pulmonary insufficiency on Doppler study in relation to the duration of diastolic turbulence in the time interval histogram.

TABLE IV

Sensitivity and Predictive Value of Pulsed Doppler and M Mode Echocardiography in Pulmonary Hypertension in the Absence of Pulmonary Stenosis

	Sensitivity		Predictive Value	
	n	%	n	%
Doppler				
TI, PI or both	60/69	87	60/69	87
TI and PI	28/69	41	28/31	90
M Mode				
RVE	26/69	38	26/28	93
PV *a* wave 2 mm or less*	18/21	86	18/20	90

* Analysis of pulmonary valve (PV) *a* wave could be performed in only 31 of 92 patients with heart disease without pulmonary stenosis.
PI = pulmonary insufficiency; RVE = right ventricular enlargement (2.8 cm or greater, left lateral recumbent position); TI = tricuspid insufficiency.

Discussion

Diagnostic specificity and sensitivity: The results of this investigation reveal that pulsed Doppler echocardiographic evidence of systolic turbulence in the right atrium and diastolic turbulence in the right ventricular outflow tract indicate tricuspid and pulmonary insufficiency, respectively. Each Doppler flow abnormality was associated with its corresponding valve lesion in the experimental animal studies. Furthermore, the presence of systolic turbulence on Doppler recording in the right atrium correlated with angiographic evidence of tricuspid insufficiency in 17 of 17 patients, with a sensitivity of 94 percent. All 12 patients with clinical features of tricuspid regurgitation and the 3 patients with a typical murmur of pulmonary insufficiency after valvotomy had Doppler evidence of tricuspid or pulmonary insufficiency, respectively. The absence of false positive findings in the patients with a normal angiogram and the absence of either tricuspid or pulmonary regurgitation on Doppler recording in the 20 patients without heart disease suggest a high clinical specificity of Doppler echocardiography for these lesions.

Unfortunately, there is no perfect "gold standard" for right-sided valve regurgitation. Cineangiography is probably extremely sensitive, but the presence of a catheter across a valve has been considered a potential source of artifactual regurgitation.[11,12] No evidence of tricuspid or pulmonary regurgitation was observed in our experimental studies on either pulsed Doppler or contrast echocardiography before surgical disruption of the valve despite the presence of a catheter across both valves. The chances of artifactual tricuspid regurgitation in our clinical angiographic studies were minimized by using an angiographic catheter with side holes, injecting at low flow rates and excluding ventricular ectopic beats from evaluation. Pulmonary angiography was not used to assess the presence of pulmonary insufficiency because of the potential risks associated with pulmonary hypertension.[23] Although contrast echocardiography with peripheral venous injection has been shown to detect tricuspid insufficiency, its sensitivity to mild degrees of insufficiency has not been validated.[24]

Comparison with left-sided regurgitant lesions: The Doppler flow disturbances described in this investigation in association with tricuspid or pulmonary insufficiency are very similar to their left-sided counterparts. Thus mitral regurgitation is associated with systolic turbulent flow in the left atrium behind the mitral valve whereas aortic insufficiency results in diastolic turbulent flow in the left ventricular outflow just below the aortic valve.[14] Previous studies from this laboratory[22] and others[17,18] comparing pulsed Doppler recording with contrast angiography established a high sensitivity and specificity of the pulsed Doppler findings to these left-sided regurgitant lesions. Because the principles of pulsed Doppler flow apply equally well (if not better by virtue of proximity of structures to the transducer) to the right side of the heart, the presence of systolic right atrial or diastolic right ventricular outflow turbulence has been presumed to indicate right-sided valve regurgitation[14]; the experimental and clinical results of our investigation further support this assumption. However, other unusual lesions may at times mimic the Doppler findings described in this investigation. Thus systolic turbulence in the right atrium may be observed in the presence of a shunt from the left ventricle to the right atrium, and diastolic turbulence in the right ventricular outflow tract may occur with a communication from the aorta to the right ventricle.

Correlation with auscultatory findings: In a simplified way, pulsed Doppler echocardiography may be considered analogous to intracardiac phonocardiography because it allows sampling within discrete intracardiac regions and thus localization of the sources of murmurs. However, although murmurs are vibrations in an audible frequency range induced by turbulent flow, the Doppler shifts represent minute changes in the frequency of reflected sound waves in an ultrahigh frequency range (megahertz) also induced by flow dynamics. Therefore, it is possible for the turbulence produced by small amounts of regurgitant flow across a relatively low pressure system (such as right ventricle to right atrium or pulmonary artery to right ventricle) to be insufficient in magnitude to induce audible vibrations but adequate to cause a frequency dispersion of the reflected sound waves. This appears to be the case in our patients in whom the incidence of tricuspid or pulmonary insufficiency on Doppler recording was considerably greater than on auscultation.

The clinical subtleties of right-sided regurgitant lesions have previously been well recognized.[2,3] Ahn and Segal[2] reported that the murmur of tricuspid insufficiency may disappear as right-sided dilatation occurs or with development of a "patent foramen ovale." The murmur of pulmonary insufficiency associated with pulmonary hypertension may mimic the murmur of aortic insufficiency.[3] There was a large incidence of aortic regurgitation in our patients, and this may have obscured the auscultatory recognition of pulmonary insufficiency.

Correlation with intracardiac pressures: Increased pressure in the right ventricle or pulmonary artery was present in 90 and 86 percent of patients with Doppler evidence of tricuspid or pulmonary insufficiency, respectively, and this finding suggests a causal relation between high pressure states and mild degrees of right-sided valve regurgitation as detected by pulsed Doppler recording. Functional tricuspid and pulmonary insufficiency have been well recognized in pressure overload states.[5,25,26] Our findings suggest that mild degrees of valve regurgitation occur more often than previously appreciated. The absence of diagnostic physical findings in many of these patients corroborates the hemodynamic insignificance of this abnormality. However, because of the frequency of its occurrence (8 percent) and the high association with pressure overload state (87 percent), pulsed Doppler detection of tricuspid or pulmonary insufficiency, or both, in the absence of

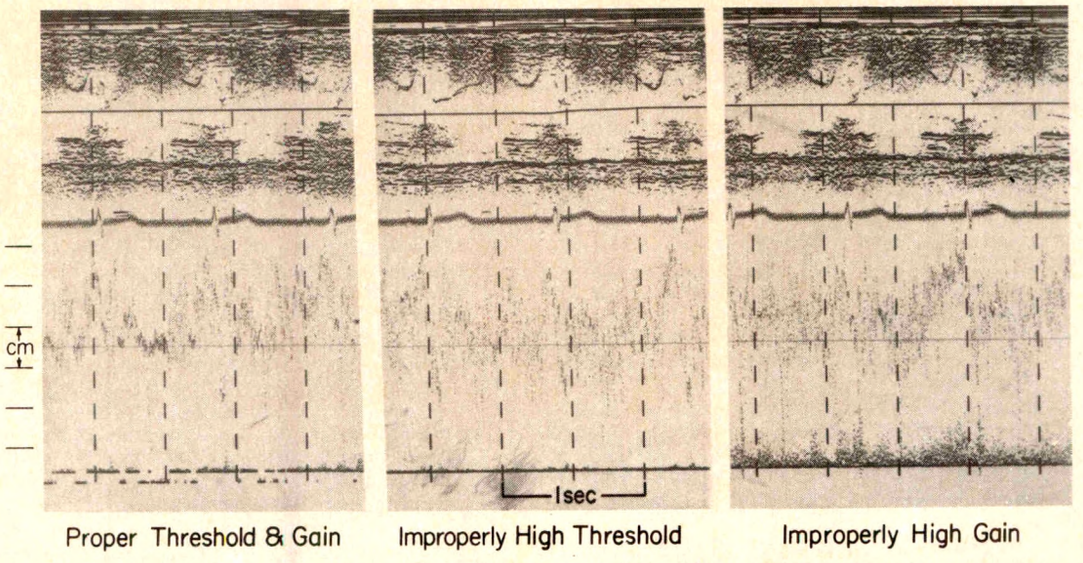

FIGURE 5. Effects of threshold and gain settings on the time interval histographic output. In the **middle and right panels,** the threshold and gain settings are inappropriately high, with excessive signals suggesting turbulence. The **left panel** shows the proper recording and appropriate threshold and gain settings in a patient without tricuspid insufficiency.

pulmonary stenosis was superior to M mode echocardiographic assessment of right ventricular size or pulmonary valve motion in the prediction of pulmonary hypertension. In addition, measurements of the duration of pulmonary insufficiency (as a fraction of diastole) allowed a gross estimation of the severity of pulmonary hypertension (mean pulmonary arterial pressure above or below 40 mm Hg).

Limitations of the technique: In its present form, pulsed Doppler echocardiography is limited in the quantification of valve regurgitation. Hemodynamically insignificant degrees of regurgitation involving any of the cardiac valves may produce frequency dispersions on the time interval histogram comparable with those seen with hemodynamically significant valve lesions. When valve regurgitation is recognized by pulsed Doppler study, other indirect echocardiographic variables (chamber size, wall motion) may be more useful to assess severity. In the case of right-sided valve regurgitation, the main clinical contribution of the pulsed Doppler technique is related to the detection of pulmonary hypertension because these lesions are often hemodynamically insignificant. Interestingly, in aortic stenosis (a high flow velocity state), pulsed Doppler assessment of the duration and amplitude of turbulence in the ascending aorta has been used successfully in differentiating aortic valve areas above from those below 1.0 cm^2[2,16].

Our use of objective analysis of the time interval histogram in this study should not imply that the technique is free of all subjectivity. A proper pulsed Doppler echocardiographic examination requires interpretation by the operator of the various audio signals emitted by cardiac valves and heart walls as well as differentiation of turbulent from nonturbulent blood flow. Moreover, proper settings of threshold and gain levels are important in obtaining the most optimal graphic display of the Doppler shifts (Fig. 5). Thus technical expertise remains an important factor in the proper use of this new noninvasive technique.

Implications: Pulsed Doppler echocardiography appears to be sensitive and specific in detecting right-sided valve regurgitation. The importance of these findings is related to the observation that in the absence of primary valve disease, evidence of tricuspid or pulmonary insufficiency, or both, on Doppler study was a frequent marker of pulmonary hypertension. This makes pulsed Doppler echocardiography superior to clinical auscultation and M mode echocardiography in the evaluation of patients in whom pulmonary hypertension is suspected.

Acknowledgment

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Quantification of Valve Regurgitation by Radionuclide Angiography Before and After Valve Replacement Surgery

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Radionuclide gated cardiac blood pool imaging was used to quantify th severity of valve regurgitation in 20 patients, by calculating the ratio left ventricular to right ventricular stroke counts (end-diastolic minu end-systolic counts in right and left ventricular regions of interest). Th ratio (the stroke index ratio) was substantially higher in patients with aort and mitral regurgitation (3.91 ± 1.45) than in a control group of 10 patien without regurgitation (1.32 ± 0.15), p <0.001. The stroke index rat correlated closely (r = 0.947) with measurements of regurgitant fracti derived from simultaneous determinations of total and forward strok volumes during cardiac catheterization.

After aortic and mitral valve replacement in 18 patients, the stroke inde ratio decreased from 4.03 ± 1.46 to 1.38 ± 0.23 (p <0.001), a value n significantly different from that observed in patients without regurgitatio All three patients with residual postoperative regurgitation had a strok index ratio greater than 2 standard deviations above the mean values f the control group (>1.62), whereas the remaining 15 patients, who ha no evidence of regurgitation, had values within the normal rang Therefore, radionuclide gated blood pool scanning provides a noninvasiv method of quantifying valve regurgitation and assessing the results medical or surgical interventions.

Evaluation of the severity of aortic and mitral regurgitation is an im portant clinical problem. Although auscultation remains the standa noninvasive method of diagnosing both the presence and the site regurgitation, quantification of the magnitude of regurgitation requir the simultaneous invasive determination of the total and forward stro volumes of the left ventricle.[1] Because of the difficulties of this metho valve regurgitation is most frequently assessed qualitatively by a su jective evaluation of the magnitude of the regurgitant jet after contra cineangiography. A less invasive and more accurate method of quan fying valve regurgitation is clearly needed.

Rigo et al.[2] recently introduced a noninvasive method of quantifyi left-sided regurgitant lesions with radionuclide angiocardiography. Wi this technique, the change in counts between diastole and systole ov the left and right ventricles is calculated and expressed as a ratio (t stroke index ratio). Because in normal persons the right ventricul stroke volume is equal to the left ventricular stroke volume, the stro index ratio should be unity in patients without regurgitant lesions a should be substantially greater than 1 in patients with significant aort or mitral regurgitation. In the study of Rigo et al., the left ventricula right ventricular stroke index ratio in normal subjects (1.15 ± 0.1 differed significantly from that in patients with mild (2.15 ± 0.48) severe regurgitation (4.00 ± 1.15). A similar relation between the r dionuclide stroke index ratio and the angiographic estimation of t magnitude of valve regurgitation was recently confirmed by Lam al.[3]

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Clinical use of this noninvasive technique requires further validation of the stroke index ratio. Previous investigations in patients correlated this ratio only qualitatively, that is, derived indexes were compared with subjective assessment of the magnitude of the angiographically visualized regurgitant jet. Validation of this ratio with electromagnetic flowmeter studies has recently been reported in dogs,[4] but a comparison with the calculated regurgitant volume derived from simultaneous measurement of total and forward stroke volumes has not been performed in human beings. Furthermore, whether the stroke index ratio improves after surgical correction of the regurgitant lesion remains to be determined. To explore these questions, we determined the stroke index ratio in a large series of patients with aortic and mitral regurgitation before and after valve replacement surgery.

Methods

Study patients: We evaluated 30 patients, whose clinical characteristics are shown in Table I. Twenty patients (10 men and 10 women, aged 23 to 72 years) had symptomatic aortic or mitral regurgitation; 18 patients in this group subsequently underwent valve replacement surgery within 1 week of angiographic evaluation. Ten patients (5 men and 5 women, aged 32 to 72 years) had cardiac catheterization for evaluation of coronary artery disease and did not have valve regurgitation, and thus served as control subjects. No patient had clinical or angiographic evidence of tricuspid regurgitation.

Calculation of the angiographic regurgitant volume and fraction: All 30 patients underwent cardiac catheterization utilizing the Sones technique. Left ventricular angiograms were performed in the right anterior oblique projection after retrograde catheterization of the left ventricle with a Sones or National Institutes of Health catheter introduced through the brachial artery. Regurgitant fraction was determined in 15 of the 20 patients with angiographically visualized aortic or mitral regurgitation. In these patients, left ventricular end-systolic and end-diastolic volumes were derived using the formula of Sandler and Dodge.[5] The total stroke volume was calculated as the difference between end-diastolic and end-systolic volumes and forward stroke volume was calculated by dividing the forward cardiac output (measured with the thermodilution technique) by the simultaneous determined heart rate. The regurgitant volume was calculated as the difference between total stroke and forward stroke volumes, and the regurgitant fraction was calculated by dividing the regurgitant volume by total stroke volume.

Calculation of the radionuclide stroke index ratio: Gated blood pool scans using technetium-99m labeled albumin (15 to 20 mCi) were performed in all 30 patients within 48 hours of cardiac catheterization. These were repeated in

TABLE I

Clinical Characteristics of Patients

Case	Age (yr) & Sex	Regurgitant Lesion	Etiology	Associated Disease
1	47F	0	—	—
2	32M	0	—	—
3	67F	0	—	1 vessel CAD
4	40F	0	—	—
5	45M	0	—	2 vessel CAD
6	72F	0	—	2 vessel CAD
7	62M	0	—	—
8	50M	0	—	—
9	72F	0	—	—
10	54M	0	—	2 vessel CAD
11	64M	AR(4+)	?	—
12*	57M	MR(4+)	MVP	—
13	40M	AR(4+)	RHD	—
14*	53F	MR(4+)	MVP	—
15	46F	MR(4+)	RHD	—
16	41M	AR(4+)	RHD	Aortic stenosis
17	54M	MR(4+)	RCT	—
18*	58F	MR(4+)	?	—
19	54F	MR(3+)	RHD	Mitral stenosis
20	66F	MR(4+)	?	—
21	39F	MR(3+),AR(3+)	RHD	Mitral stenosis
22	66M	MR(4+)	PMD	2 vessel CAD
23†	72F	AR(3+)	?	—
24†	44F	AR(2+)	?	Mitral stenosis
25	25M	MR(2+)	RHD	Mitral stenosis
26	64F	AR(2+)	BAV	Aortic stenosis
27*	23M	AR(4+)	?	—
28	37F	MR(3+)	RHD	—
29*	63M	AR(4+),MR(1+)	RHD	1 vessel CAD
30	39M	AR(4+),MR(1+)	RHD	—

* Regurgitant fraction not determined in these five patients.
† Valve replacement surgery not performed in these two patients.
AR = aortic regurgitation; BAV = bicuspid aortic valve; CAD = coronary artery disease; MR = mitral regurgitation; MVP = mitral valve prolapse; PMD = papillary muscle dysfunction; RCT = ruptured chordae tendineae; RHD = rheumatic heart disease. Numbers in parentheses refer to angiographic grade of regurgitation.

the 18 patients with valve regurgitation who had valve replacement surgery 7 to 10 days postoperatively. Acquisition was performed in the 40 to 45° left anterior oblique projection using an Ohio Nuclear sigma microprocessor 550 camera with an 18 parallel hole 1 inch (2.54 cm) thick collimator, acquiring a density of 256 counts/pixel in the left ventricle. For each patient, the angle of the projection was optimized for best separation of the left and right ventricles, but no caudal tilt was used. Data were recorded using a continuous electrocardiographically synchronized mode with 16 frames scanning the cardiac cycle. The total acquisition time was 7 to 8 minutes.

Regions of interest were drawn over the right and left ventricles and right and left atria. The regions of interest were defined by visual inspection and were fixed throughout the time course of systole and diastole. Background subtraction was not performed. The entire time-activity curve was displayed from each chamber to minimize atrioventricular overlap; diastolic and systolic periods were selected separately for each ventricle at the peak and nadir of each ventricular curve.

Derived variables were calculated as follows: (1) Ventricular stroke counts index = change in counts between systole and diastole in the ventricular region of interest. (2) Stroke index ratio = left ventricular stroke counts index/right ventricular stroke counts index.

Statistical analysis: The stroke index ratio before surgery in the 20 patients with valve regurgitation was compared with that of the 10 patients without regurgitation by means of the *t* test for independent variables. The regurgitant fraction determined during cardiac catheterization in 15 patients was tested for possible relation to the stroke index ratio determined from radionuclide angiocardiography by least squares linear regression analysis. Pre- and postoperative values for the stroke index ratio were compared in the 18 patients who had valve replacement surgery by means of the *t* test for paired data. Group data are expressed as mean values standard deviation.

Results

The stroke index ratio in the 20 patients with angi graphically demonstrated aortic or mitral regurgitatio or both (mean 3.91 ± 1.45, range 1.84 to 6.73) was si nificantly higher than that in the control group of patients without regurgitation (mean 1.32 ± 0.15, ran 0.99 to 1.49 ($p < 0.001$). In the 15 patients whose regu gitant fraction was calculated by simultaneous dete minations of total and forward stroke volumes duri cardiac catheterization, the stroke index ratio varie linearly and directly with the regurgitant fraction (r 0.947, $p < 0.001$) (Fig. 1).

Effect of valve replacement: After aortic and mitr valve replacement, the stroke index ratio decrease from 4.03 ± 1.46 to 1.38 ± 0.23 ($p < 0.001$, $n = 18$), value not significantly different from that observed our control patients without regurgitation (Fig. 2 Fifteen patients had no clinical evidence for residu valve regurgitation postoperatively and had strol index ratios of 1.03 to 1.49. Three patients had clinic evidence of regurgitation postoperatively; (in two p tients with aortic valve replacement a perivalve le

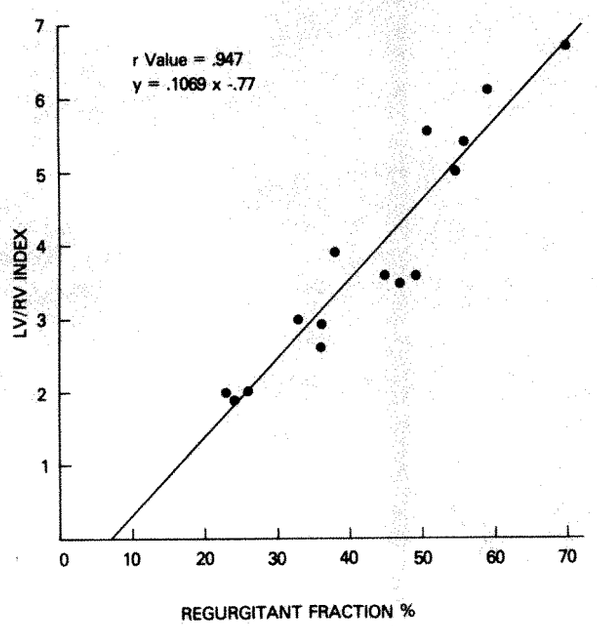

FIGURE 1. Correlation in 15 patients between left ventricular/right ventricular (LV/RV) stroke index ratio derived from radionuclide imaging and regurgitant fraction calculated by simultaneous determinations of the total and forward stroke volumes during cardiac catheterization.

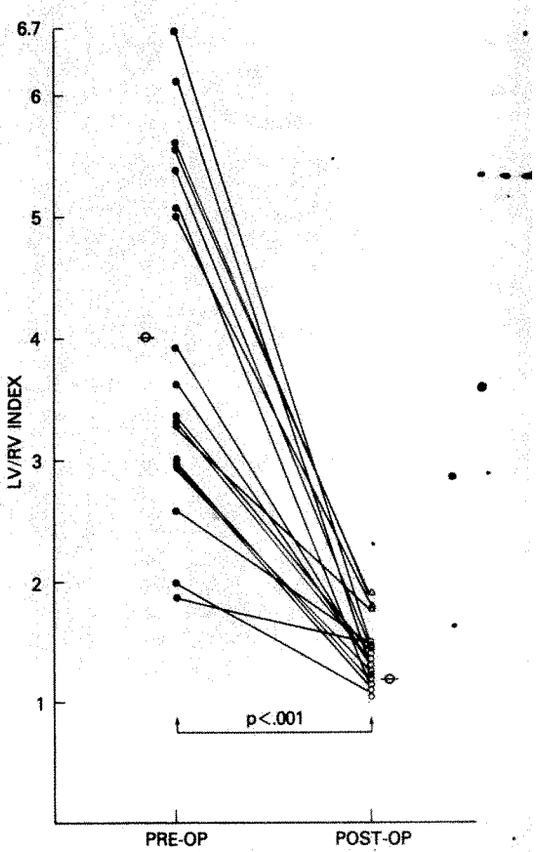

FIGURE 2. Values for left ventricular/right ventricular (LV/RV) stro index ratio preoperatively (PRE-OP, **closed symbols**) and postoperativ (POST-OP, **open symbols**) in 18 patients who underwent valve placement surgery. Of these, three patients had residual valve reg gitation (**triangles**), and 15 patients did not (**circles**).

developed, and in one patient with severe aortic and mild mitral regurgitation preoperatively only the aortic valve was replaced). All three patients had a postoperative stroke index ratio (1.7 to 1.9) that was greater than 2 standard deviations above the mean values for our control group (>1.62).

The intraobserver agreement for determination of the stroke index ratio calculated from independent measurements made without knowledge of the catheterization data or the pre- or postoperative status of the images was excellent (r = 0.98).

Discussion

Our study validates the use of the stroke index ratio determined with radionuclide angiocardiography as an estimate of the magnitude of valve regurgitation in patients with aortic or mitral valve disease, or both. Preliminary studies[2,3] have previously shown a good relation between the stroke ratio index and qualitative estimates of angiographic regurgitation.[2,3] Our present data extend these findings and establish a linear relation between the index and quantitative calculations of the regurgitant fraction in man. Furthermore, our data indicate that the stroke index ratio is significantly reduced toward the normal range by surgical correction of the valve lesion. A stroke ratio index greater than 1.62 indicates significant valve regurgitation preoperatively and suggests residual regurgitation postoperatively.

Limitations of the method: Despite these encouraging results, the technique has major limitations in detecting and quantifying mild degrees of regurgitation. We and others[2,3] have found that the stroke index ratio in normal subjects was higher than the expected value of 1.0, so that the ratio in patients with mild degrees of regurgitation might occasionally fall into the normal range. Previous investigations[3] have established that this is most likely due to incomplete separation of the right and left ventricles from the surrounding structures, because in the left anterior oblique projection the atria are superimposed on a portion of the ventricular regions of interest, the degree of overlap being variable during different parts of the cardiac cycle. For this reason, in this study, only ratios greater than 1.62 exceeded 2 standard deviations above the mean value of our control group. This value (which corresponds to a regurgitant fraction of 22 percent (Fig. 1) represents the mildest degree of regurgitation that can be detected with certainty. It is similar to the 30 percent value suggested by Rigo et al.,[2] who used similar methods. However, use of a slant hole collimator with a 30° caudal tilt can reduce the degree of overlap and narrow the range for normal subjects for the stroke index ratio toward unity[3]; this would facilitate detection of smaller degrees of regurgitation. Further validation of this technique in patients with marked dilatation of atrial or ventricular chambers needs to be done.

Applications of the method: advantages over ejection fraction: The ability to estimate the magnitude of regurgitation substantially increases the value of radionuclide angiography in the evaluation of cardiac performance in a variety of cardiac disorders. Although the reliability of radionuclide studies in the measurement of ejection fraction is well established,[7] the ejection fraction frequently poorly reflects the hemodynamic and clinical characteristics of patients with significant regurgitant lesions. Whereas the ejection fraction correlates well with the hemodynamic and clinical results in patients who undergo coronary bypass surgery,[8,9] it often decreases after mitral valve replacement for valve regurgitation despite an improvement in forward output, reduction in pulmonary congestion and marked amelioration of dyspnea and fatigue.[10,11] Conversely, the ejection fraction may rise after the onset of acute mitral regurgitation secondary to a perivalve leak due to the creation of a low impedance leak,[12] despite severe hemodynamic and symptomatic deterioration. Furthermore, significant decreases in regurgitant volume may accompany the administration of peripheral vasodilators to patients with valve regurgitation, although changes in ejection fraction are frequently insignificant.[13–15] These reductions may explain in part why vasodilator therapy is often unaccompanied by changes in radionuclide ejection fraction despite hemodynamic and clinical improvement[13,16]; in such cases, estimation of the magnitude of regurgitation by the methods described in this study may reveal significant benefit not reflected by a consideration of ejection fraction alone.

In conclusion, radionuclide angiography provides a noninvasive method of detecting and quantifying the magnitude of left-sided valve regurgitation by the use of a method that compares left ventricular and right ventricular systolic and diastolic counts. This method has great potential clinical utility in the long-term follow-up of asymptomatic patients with mitral or aortic insufficiency, or both, and in the evaluation of the results of medical and surgical interventions.

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Radionuclide Regurgitant Index: Value and Limitations

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The radionuclide regurgitant index, defined as left ventricular/right ventricular stroke counts obtained from gated equilibrium studies, has been reported to predict the presence and severity of left-sided valve regurgitation. This study evaluated the radionuclide regurgitant index in 100 patients in whom left-sided valve regurgitation was angiographically graded (0 to 4+) with regard to most severe mitral or aortic regurgitation. Regurgitation was graded 0 in 44 of the 100 patients, 1+ in 22, 2+ in 8, 3+ in 6 and 4+ in 20.

The radionuclide regurgitant index was 0.9 to 1.5 in 51 patients, 1.6 to 2.4 in 23 and 2.5 to 12.0 in 26. The mean radionuclide regurgitant index was 1.34 in the group with no regurgitation and 1.60 in those with 1+, 2.01 in those with 2+, 2.80 in those with 3+ and 3.85 in those with 4+ regurgitation. There was a significant difference ($p < 0.05$) in the radionuclide regurgitant index between patients with no regurgitation and each group with regurgitation and between groups with regurgitation separated by two or more grades of angiographic regurgitation.

Twelve patients had a discordant radionuclide regurgitant index; their index either predicted clinically significant or severe regurgitation when they had no or trivial regurgitation, or predicted no or trivial regurgitation when they had clinically significant regurgitation. Eight of 10 patients with a left ventricular ejection fraction of less than 0.30 had a discordant index ($p < 0.0005$). All three patients with mitral valve prolapse associated with frequent ventricular extrasystoles had a discordant index ($p < 0.0005$).

Recently, gated radionuclide equilibrium studies have been utilized as a noninvasive technique for measuring the severity of valve regurgitation. Rigo et al.[1] reported a radionuclide index of left-sided valve regurgitation derived from gated cardiac blood pool studies. This index was defined as the ratio of left to right ventricular stroke counts, calculated from the difference in counts in each ventricle between end-diastole and end-systole. On the basis of studies in 40 patients (31 with cardiac catheterization), they suggested that this index was useful in assessing the presence and severity of aortic or mitral regurgitation, or both.

In this study, we measured the radionuclide regurgitant index in 100 patients undergoing both cardiac catheterization and electrocardiographically synchronized radionuclide cardiac studies in an attempt to assess further the utility of this new noninvasive measure of left-sided valve regurgitation. In addition, we attempted to define subgroups of patients whose radionuclide regurgitant index appeared to predict spuriously the presence or absence of significant regurgitation.

Methods

Patient selection: The study group consisted of 100 consecutive patients undergoing clinically indicated diagnostic cardiac catheterization and radionuclide cardiac equilibrium studies. The catheterization and radionuclide studies were performed within a period of 2 weeks in all patients and within 3 days in 66 patients. There was no change in the clinical or hemodynamic status of any patient between the two studies. Patients were excluded from consideration and

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were not included in this analysis if they had an intracardiac shunt or clinically evident tricuspid regurgitation.

Angiographic studies: The angiographic methods included biplane left cineventriculography (30° right anterior oblique and 60° left anterior oblique projections) in all patients, and ascending aortography (45° left anterior oblique projection) for aortic regurgitation when clinically indicated. The severity of mitral and aortic regurgitation was angiographically graded (only during conducted beats) by consensus of two of us on a 0 to 4+ scale modified from Sellers et al.[2] The grading scale was as follows: 0 = no regurgitation visualized; 1+ = slight opacification of the proximal chamber clearing completely in one cycle; 2+ = moderate opacification of the proximal chamber not completely clearing in one cycle but without progressive opacification; 3+ = progressive opacification of the proximal chamber over three or more cycles; 4+ = total opacification of the proximal chamber within one or two cycles.

For purposes of this study, patients with combined aortic and mitral regurgitation were categorized according to the most severe lesion. This categorization, rather than algebraic addition of graded aortic and mitral regurgitation, was utilized because the angiographic grading is not necessarily a linear function for which addition would be appropriate. For example, the severity of regurgitation in a patient with 2+ aortic and 2+ mitral regurgitation is not necessarily the same as that in a patient with a 4+ mitral regurgitation, and is of less clinical importance.

Radionuclide studies: The radionuclide cardiac studies were performed with 15 to 25 mCi of technetium-99m in vivo labeled red blood cells.[3] A large field of view Anger camera with a low energy all-purpose collimator was positioned in the left anterior oblique projection, chosen for best visualization of the ventricular septum, with a 10° to 15° caudal tilt. The electrocardiographically synchronized cardiac equilibrium study was acquired onto a dedicated mini-computer SIMIS-III (Informatek State, Inc., Norcross, Georgia), in 16 frames of 64 by 64 matrix resolution. Acquisition was continued until there were 500,000 counts/frame. Frame duration ranged from 30 to 60 ms depending on the patient's heart rate. The left ventricular ejection fraction was calculated in a standard manner previously described.[4]

For calculation of the regurgitant index, the end-diastolic frame was considered the first frame after the R wave. The end-systolic frame was taken from the nadir of the left ventricular time-activity curve derived during the calculation of ejection fraction. A region of interest for each ventricle in end-diastole (drawn by consensus of three of us) was utilized to calculate the regurgitant index. These regions of interest were drawn on simultaneously displayed end-diastolic and end-systolic frames, and on subtraction images (obtained from subtracting the end-systolic from the end-diastolic frame and vice versa) using a double cursor technique.[5] For the right ventricle, the subtraction images were particularly useful for delineating the right ventricular region of interest. In this way, the best delineation of the boundary between the right atrium and right ventricle was possible (Fig. 1). The left ventricular region of interest was actually obtained during the ejection fraction processing so that the determination of the regurgitant index added only a small amount to the overall processing time. *The regurgitant index was calculated by the following formula:*

$$\text{Regurgitant index} = \frac{\text{LV stroke counts}}{\text{RV stroke counts}},$$

where LV stroke counts = (counts in end-diastolic frame from left ventricular end-diastolic region of interest) minus (counts in end-systolic frame from left ventricular end-diastolic region of interest), and right ventricular stroke counts = (counts in end-diastolic frame from right ventricular end-diastolic region of interest) minus (counts in end-systolic frame from right ventricular end-diastolic region of interest).

FIGURE 1. Delineation of right and left ventricular regions of interest for calculation of the radionuclide regurgitant index is performed on simultaneously displayed end-diastolic (**a**), end-systolic (**b**) and subtraction images [end-diastole minus end-systole (**c**) and end-systole minus end-diastole (**d**)].

Thus, no background was subtracted in this calculation and the same end-diastolic and end-systolic frames were used for both ventricles. Also, only the end-diastolic regions of interest were utilized for counts from the ventricles in end-systole as well as end-diastole.

Statistical analysis: The calculation of the radionuclide regurgitant index and angiographic grading were performed independently. The radionuclide regurgitant index was compared with angiographically graded regurgitation using a logarithmic transformation and one way analysis of variance. The chi-square test with the Yates correction was utilized to compare patient subgroups.

Results

Patient characteristics: Of the 100 patients studied, 57 were male and 43 female; their ages ranged from 14 to 73 years (mean ± standard deviation 44.6 ± 16.3 years). Table I lists the cardiac diagnosis in these 100 patients. Ninety-four patients had sinus rhythm, including 16 patients who had frequent (6 or more/min) ventricular extrasystoles. Six patients had chronic atrial fibrillation.

TABLE I

Cardiac Diagnoses of Study Group

Diagnosis	Patients (n)
No structural heart disease	14
Coronary artery disease	25
Rheumatic heart disease	21
Primary myocardial disease	16
Mitral valve prolapse	11
Bacterial endocarditis	5
Other valvular heart disease	6
Other nonvalvular heart disease	2
Total	100

The left ventricular ejection fraction obtained from the radionuclide study ranged from 0.15 to 0.82 (mean 0.55 ± 0.16). Left ventricular ejection fraction was greater than 0.50 in 68 patients, between 0.30 and 0.50 in 22 patients and less than 0.30 in 10 patients.

Angiographic regurgitation: Angiography demonstrated no left-sided regurgitation in 44 patients, mitral regurgitation in 29, aortic regurgitation in 14 and both mitral and aortic regurgitation in 13 patients.

Among the 56 patients with regurgitation, the regurgitation was graded 1+ in 22, 2+ in 8, 3+ in 6 and 4+ in 20. The 56 patients included 4 patients with frequent ventricular extrasystoles (3 with 1+, 1 with 2+ regurgitation) and 3 patients with atrial fibrillation (1 with 1+, 1 with 2+ and 1 with 4+ regurgitation).

Radionuclide regurgitant index: For the entire study group, the radionuclide regurgitant index ranged from 0.9 to 12.0 (mean of 1.86; range encompassing mean ±1 SD 1.31 to 2.64). The regurgitant index ranged from 0.9 to 1.5 in 51 patients and from 1.6 to 2.4 in 23; it was 2.5 or greater in 26 patients.

Figure 2 presents the regurgitant index for all patients as a function of angiographically graded regurgitation. Table II lists the mean regurgitant index for each group of angiographically graded regurgitation.

There was a statistically significant difference ($p < 0.05$) between the regurgitant index of the group with no regurgitation and that of each group with regurgitation. In groups with regurgitation, the regurgitant index did not differ significantly between adjacent grades; however, there was a significant difference between groups separated by more than one grade (that is, 1+ versus 3+ or 4+, and 2+ versus 4+).

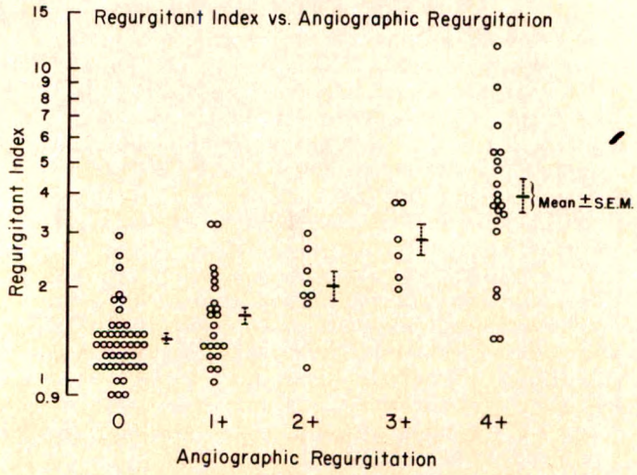

FIGURE 2. The radionuclide regurgitant index (on a logarithmic scale) is compared with the grade of angiographic regurgitation. Each patient is represented by an **open circle. Bar markers** indicate the mean and standard error of the mean (S.E.M.) for each angiographic grade. See text for discussion.

Predictive accuracy of the regurgitant index: Table III demonstrates the ability of a regurgitant index of 1.5 or less to predict no or trivial regurgitation (0 or 1+), and a regurgitant index of greater than 1.5 to predict the presence of clinically significant regurgitation (2+, 3+ or 4+).

Ninety-four percent (48 of 51) of patients with a regurgitant index of 1.5 or less had no or trivial regurgitation; 37 percent (18 of 49) of patients with a regurgitant index greater than 1.5 had no or trivial regurgitation, and 63 percent (31 of 49) had significant regurgitation. Conversely, 73 percent (48 of 66) of patients with no or trivial regurgitation had a regurgitant index of 1.5 or less (chi-square = 34, $p < 0.0005$). Thus, a regurgitant index of 1.5 or less is a very specific (94 percent) but less sensitive (73 percent) indicator for detecting the absence of significant regurgitation.

TABLE II

Radionuclide Regurgitant Indexes in Each Grade of Angiographic Regurgitation

Angiographic Grade	Radionuclide Regurgitant Indexes			
	Range	Mean	Mean ±1 SD	Mean ±1 SEM
0	0.9–2.9	1.34	1.04–1.71	1.29–1.39
1+	1.0–3.2	1.60	1.16–2.21	1.50–1.72
2+	1.1–3.0	2.01	1.49–2.72	1.81–2.24
3+	2.0–3.8	2.80	2.13–3.67	2.51–3.13
4+	1.4–12.0	3.85	2.22–6.65	3.41–4.35

SD = standard deviation; SEM = standard error of the mean.

TABLE III

Predictive Value of the Radionuclide Regurgitant Index for Clinically Significant and Severe Regurgitation

Radionuclide Regurgitant Index	Patients With No or Trivial (0, 1+) Regurgitation (n)	Patients With Significant (2+, 3+, 4+) Regurgitation (n)	Total
≤1.5	48	3	51
>1.5	18	31	49
Total	66	34	100
	Patients With Nonsevere (0, 1+, 2+) Regurgitation (n)	Patients With Severe (3+, 4+) Regurgitation (n)	
<2.5	68	6	74
≥2.5	6	20	26
Total	74	26	100

Table III demonstrates the ability of a regurgitant index of 2.5 or greater to predict the presence of clinically severe regurgitation (3+ or 4+) and a regurgitant index of less than 2.5 to predict the absence of severe regurgitation (0, 1+ or 2+).

Seventy-seven percent (20 of 26) of patients with a regurgitant index of 2.5 or greater had severe regurgitation; 92 percent (68 of 74) of patients with a regurgitant index of less than 2.5 did not have severe regurgitation. Conversely, 77 percent (20 of 26) of patients with severe regurgitation had a regurgitant index of 2.5 or greater (chi-square = 45, $p < 0.0005$). Thus, a regurgitant index of 2.5 or greater was a relatively sensitive (77 percent) and specific (77 percent) indicator of severe regurgitation.

Clinical characteristics of patients with a discordant regurgitant index: The regurgitant index was arbitrarily defined as discordant if it was greater than 1.5 in patients with no regurgitation or greater than 2.5 in patients with 1+ regurgitation (Fig. 3). In patients with 2+, 3+ and 4+ regurgitation, the regurgitant index was also arbitrarily defined as discordant if it was 1.5 or less.

Twelve patients had a discordant regurgitant index. Nine of these had false positive discordance (that is, a regurgitant index predicting significant or severe regurgitation in patients with no or trivial regurgitation). Three of these nine patients had both mitral valve prolapse and frequent ventricular extrasystoles, five had a left ventricular ejection fraction of less than 0.30, and one had coronary artery disease with an ejection fraction of 0.47.

Three patients had false negative discordance (that is, a regurgitant index predicting no or trivial regurgitation in patients with significant regurgitation). All three had a left ventricular ejection fraction of less than 0.30.

Table IV presents the incidence of discordance in specific patient groups. There was a significant association of discordance with a left ventricular ejection fraction of less than 0.30 and with mitral valve prolapse associated with frequent ventricular extrasystoles. Patients with frequent ventricular extrasystoles alone (without an ejection fraction of less than 0.30 or mitral valve prolapse), atrial fibrillation or mitral valve prolapse without frequent ventricular extrasystoles did not have a discordant regurgitant index.

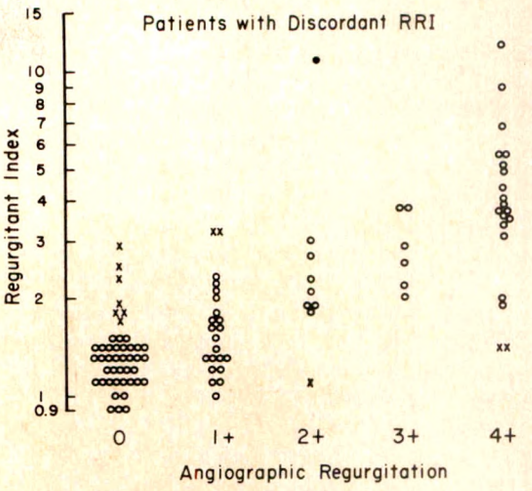

FIGURE 3. The radionuclide regurgitant index (RRI) is compared with the grade of angiographic regurgitation as in Figure 2. Patients with a regurgitant index considered discordant (see text for discussion) are represented by **crosses.** The remaining patients, whose regurgitant index was not discordant, are represented by **open circles.**

Discussion

Gated cardiac blood pool studies have previously been validated for the noninvasive evaluation of right and left ventricular function.[6–10] These studies have been demonstrated to be useful for measuring ventricular ejection fraction and assessing regional wall motion abnormalities. Recently, Rigo et al.[1] proposed the ratio of left to right ventricular stroke counts (defined as the difference between end-diastolic and end-systolic counts for each ventricle) as a measurement of the presence and severity of left-sided valve regurgitation. In their patients with significant mitral or aortic regurgitation, or both, the ratio of left to right ventricular stroke counts was significantly greater than unity. In their patients without regurgitation, this ratio ranged from 0.9 to 1.4 (mean 1.15). Baxter et al.[11] provided quantitative verification of this hypothesis utilizing a dog model with experimentally induced acute aortic regurgitation. Bough et al.[12] recently reported reasonable correlation of this stroke count ratio with quantitative catheterization methods.

Rigo et al.[1] demonstrated that this ratio of left to right ventricular stroke counts, or regurgitant index, was

TABLE IV

Incidence of Discordant Radionuclide Regurgitant Indexes

	Patients in Total Series (n)	Patients With Index Discordant		p Value*
		n	%	
Entire study group	100	12	12	
Ejection fraction <0.30	10	8	80	<0.0005
Mitral prolapse without PVCs	8	0	0	NS
PVCs without mitral prolapse	13	2†	15	NS
Mitral prolapse with PVCs	3	3	100	<0.0005
Atrial fibrillation	6	0	0	NS

* Probability (p) value of chi-square test comparing presence of discordance and presence or absence of clinical characteristic listed.
† Two patients with PVCs without mitral prolapse with a discordant regurgitant index had an ejection fraction of less than 0.30.
NS = not significant; PVCs = frequent ventricular contractions.

reproducible when calculated by different observers. Because we also have found little interobserver variability in calculation of the radionuclide regurgitant index, we did not formally repeat this study. Rigo et al. showed a significant correlation between the regurgitant index and the severity of left-sided valve regurgitation in 40 patients (of whom 31 underwent catheterization and 20 manifested regurgitation of varying degrees of severity). There was no overlap in the regurgitant indexes calculated in patients with no regurgitation and in those with moderate or severe regurgitation. The patients studied had good overall left ventricular function, only four having a reduced left ventricular ejection fraction (less than 0.50).

Methodologic considerations: In this study, we attempted to assess the usefulness of the radionuclide regurgitant index in a variety of cardiac disorders, rhythms and ranges of cardiac function. Our radionuclide method was based on the principle outlined by Rigo et al.[1] utilizing a single end-diastolic region of interest for each ventricle without background subtraction. Our technique differed from that of Rigo et al. because we used (1) in vivo labeled red blood cells rather than labeled albumin[3]; (2) a caudal tilt in the left anterior oblique position; (3) subtraction images (including end-diastole minus end-systole and end-systole minus end-diastole)[5,8,9]; and (4) the continuous electrocardiographically synchronized equilibrium mode of acquisition for all studies.[4] The use of the caudal tilt allowed improved separation of the atria from the ventricles, especially in the right side of the heart. Subtraction images, especially the "stroke volume image" (obtained from the subtraction of end-systole from end-diastole), aided in the delineation of the right and left ventricular regions of interest. The radionuclide methods we utilized are virtually identical to the methods used in the recent report of Bough et al.[12] However, Bough et al. utilized a 30° caudal slant hole collimator of intermediate sensitivity as opposed to a caudal tilt.

We applied the continuous electrocardiographically synchronized mode of acquisition and display to all patients studied. Rigo et al.[1] applied this mode of display in only 19 of 40 patients. For simplicity, we utilized only the nadir of the left ventricular time-activity curve in identifying the end-systolic frame for both ventricles. Although there is a potential for error because right and left ventricular end-systole may not coincide, Rigo et al. found no systematic difference between using the same end-systolic frame for both ventricles as opposed to using separate time-activity curves to identify each ventricular end-systole.

In our method, the cardiac cycle was divided into 16 frames. Theoretically, increasing the number of frames would appear to increase the accuracy of the regurgitant index because the peak and nadir of time-activity curves would be sharper. However, to obtain the same number of overall counts/frame, a longer acquisition time would be necessary because the time interval of each frame would be shorter. Otherwise, for the same acquisition time, increasing the number of frames would result in a lower number of counts/frame and more statistical variation.

Correlation of radionuclide and angiographic regurgitation: In our series, the radionuclide regurgitant index generally correlated with the presence and severity of angiographic left-sided valve regurgitation. There was a significant difference between the regurgitant index of patients without angiographic regurgitation and that of patients with 1+ or greater regurgitation. There was no significant difference between the indexes of patients with adjacent angiographic grades of regurgitation, a finding that may reflect the small number of patients with angiographically graded 2+ and 3+ regurgitation. Comparison of the regurgitant indexes of patients separated by more than one grade of regurgitation (that is, 1+ versus 3+, 2+ versus 4+) showed a significant difference.

A regurgitant index of 1.5 or less generally indicated no or trivial regurgitation. This separation was more specific (94 percent) than it was sensitive (73 percent). A regurgitant index of 2.5 or greater was a relatively sensitive (77 percent) and specific (77 percent) predictor of severe regurgitation. Patients with a regurgitant index between 1.5 and 2.4 had a wide range of angiographic regurgitation. Generally, they had 0, 1+ or 2+ regurgitation rather than 3+ or 4+ regurgitation, but this trend did not appear to be of statistical significance.

Causes of discrepancies between angiographic grading and regurgitant index: Unlike the patients studied by Rigo et al.,[1] our patients demonstrated some overlap in the range of regurgitant indexes in all angiographic grades of regurgitation. The study by Bough et al.[12] illustrated some discrepancies between the angiographic grading and the radionuclide assessment of the severity of valve regurgitation; however, there was no explanation of these discrepancies. In attempting to identify the characteristics of patients whose regurgitant index appeared to be obviously discordant, we examined a group of arbitrarily classified patients on the basis of regurgitant indexes shown to separate no and trivial from significant regurgitation, and severe from nonsevere regurgitation. Patients with a greatly reduced left ventricular ejection fraction (less than 0.30) had a significantly greater incidence of discordance than did patients with an ejection fraction of 0.30 or greater. We can only postulate why the regurgitant index appears to predict inaccurately the presence or severity of regurgitation in patients with a greatly decreased left ventricular ejection fraction. Such patients generally have elevated pulmonary arterial pressures or right ventricular failure and may have clinically silent tricuspid regurgitation. These conditions would tend to reduce the radionuclide regurgitant index in patients with significant left-sided regurgitation. Conversely, the severity of regurgitation may be overestimated angiographically in these patients because of a relatively slow washout of contrast medium with a greatly reduced forward output. These explanations would not account for the discrepancies noted in patients with a low ejection fraction, no angiographic regurgitation and a high

regurgitant index. The precision with which the stroke counts can be measured may be reduced in patients with low right and left ventricular ejection fractions and markedly dilated ventricular chambers. This factor may account for these discrepancies.

Limitations of method and sources of error: The inability of the radionuclide regurgitant index to detect the presence of severity of regurgitation in patients with a very low ejection fraction limits its usefulness in assessing the significance of a mitral regurgitant murmur in these patients. Thus, the regurgitant index would not be able to discriminate adequately between a patient with a cardiomyopathy with mild mitral regurgitation (secondary to distortion of the supporting structures of the mitral valve) and a patient with severe long-standing mitral regurgitation with resultant depressed left ventricular dysfunction (secondary to the volume overload) if the ejection fraction was less than 0.30.

All three patients with mitral valve prolapse associated with frequent ventricular extrasystoles had a high regurgitant index in the absence of angiographic mitral regurgitation during conducted beats. There were eight patients with mitral valve prolapse alone and 11 patients with frequent ventricular extrasystoles alone (without either prolapse or a greatly reduced ventricular ejection fraction). None of these patients had a discordant regurgitant index. Possibly, the patients with both mitral valve prolapse and frequent ventricular extrasystoles had mitral regurgitation with extrasystoles during the radionuclide study that was not noted during angiography (when only conducted beats were analyzed). The presence of atrial fibrillation did not invalidate the regurgitant index.

This radionuclide method is also theoretically limited in clinical conditions with volume overload of the right ventricle such as tricuspid regurgitation or atrial septal defect. Also, the method does not allow discrimination of aortic from mitral regurgitation.

Previous angiographic studies have demonstrated nearly equal right and left ventricular stroke volumes in the absence of shunts and valve regurgitation.[13] It was not immediately clear why the regurgitant index was greater than 1.0 in some patients with no regurgitation. It is more difficult to separate the right atrium from the right ventricle than it is to separate the left atrium from the left ventricle in the radionuclide study. Because the right atrial time-activity curve peaks during right ventricular systole, inclusion of a portion of the right atrium in the right ventricular region of interest would result in a dampening of the right ventricular time-activity curve. This reduction in the right ventricular stroke counts would systematically increase the ratio of left to right ventricular stroke counts.

There may be other geometric factors that may resul in different absorption characteristics of each ventric ular blood pool. Reported data[12,14] suggest that bette separation of the atria from the ventricles with a 30 slant hole collimator results in regurgitant indexes close to unity and with less variability (1.00 ± 0.08) in pa tients with no regurgitation. We were able to obtain onl a 10° to 15° caudal angulation, a factor that might ex plain our higher values. Our mean value for regurgitan index (1.34) was also higher than that (1.15) reporte by Rigo et al. for patients with no regurgitation. Ou method utilized a 10° to 15° caudal tilt, whereas Rig et al. did not utilize any caudal tilt. Thus, the caudal til would not appear to explain the difference in this in stance. Our inclusion of patients with a wider range c cardiac function (including patients with a discordan index and a low ejection fraction) than that of patient in the study by Rigo and co-workers may explain th difference.

Limitations of angiographically graded re gurgitation: Unfortunately there is no ideal "gol standard" for the quantitation of valve regurgitation Angiographically graded regurgitation is the metho most widely utilized clinically. This visual grading c angiographic regurgitation is affected by the size of th ventricular and atrial chambers. Regurgitant fraction can be calculated by comparing the angiographic le ventricular stroke volume with the forward stroke vo ume calculated from the cardiac output and heart rat The presence of any arrhythmia during angiograph invalidates this calculation because only a few beats ar available for analysis. The angiographically calculate regurgitant fraction also is subject to the limitations c calculating the stroke volumes with angiography an with cardiac output determinations. This limitation a particular problem in patients with a very low cardia output and stroke volume and large ventricular vo umes. Limiting analysis to patients in whom a mea surement of an angiographic regurgitant fraction wa possible or whose regurgitant index corresponded to th angiographic grading would preselect patients and thu might lead to false conclusions of the accuracy of th radionuclide regurgitant index.

Implications: The radionuclide regurgitant index useful for assessing the presence and severity of lef sided valve regurgitation. The presence of a marked reduced left ventricular ejection fraction may result both false positive and false negative discordan regurgitant indexes. Mitral valve prolapse associate with frequent ventricular extrasystoles may result in false positive discordant regurgitant index. Recognizin these potential sources of error should make the r dionuclide regurgitant index more useful.

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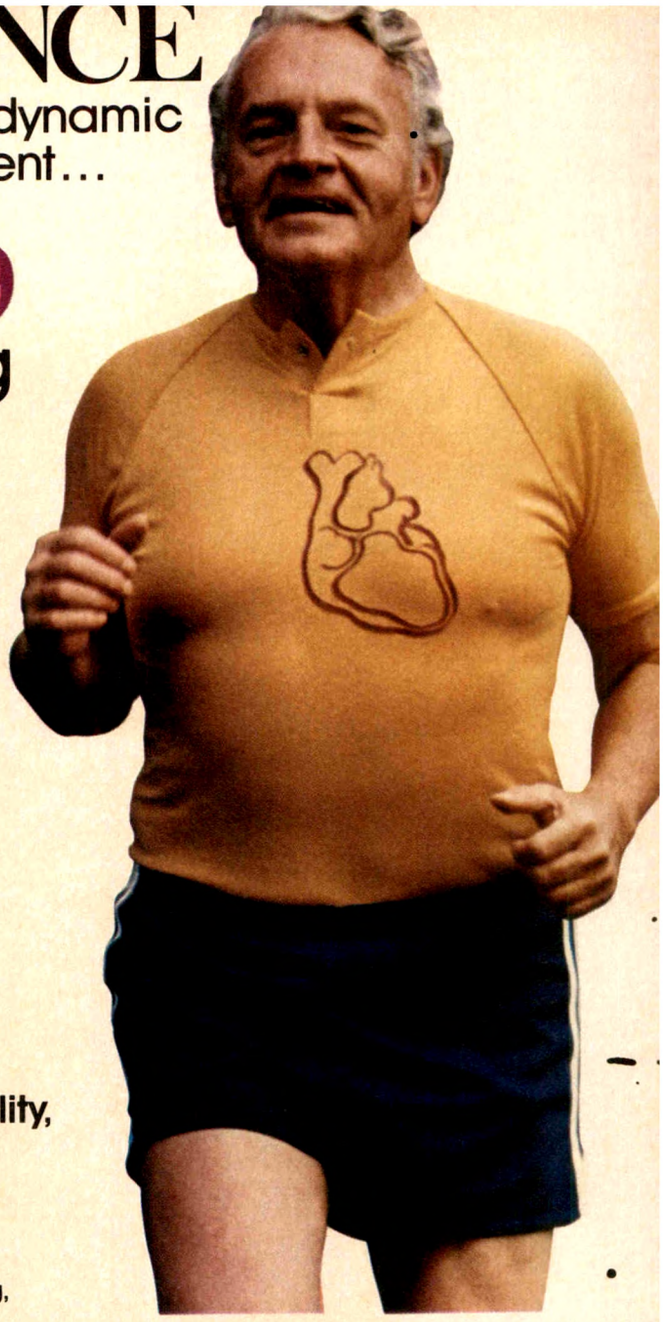

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DOSAGE AND ADMINISTRATION: Administer the smallest effective dose two or thre times daily at 8- to 12-hour intervals, unless clinical response suggests a differe regimen. Patient should be titrated to anginal relief or hemodynamic response. Hemo dynamic response can be measured by drop in systolic blood pressure. Discontinue not effective.

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DESCRIPTION
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INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS
Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C78-23 (4/78)

Consult complete product literature before prescribing. 128-6089-A

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Intermedics Pulse Generators

INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symptomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

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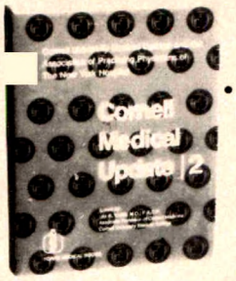

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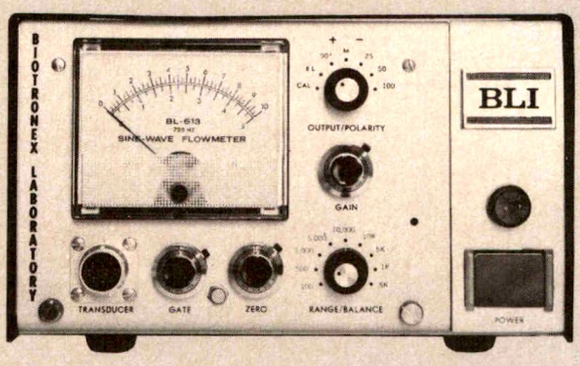

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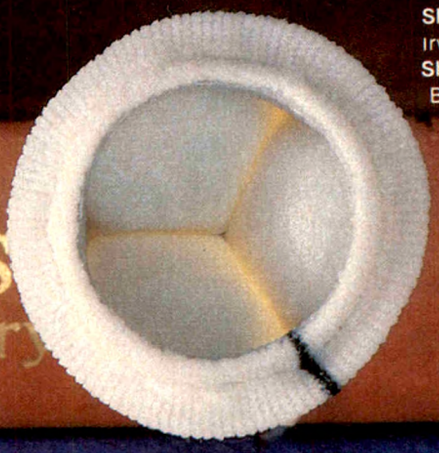

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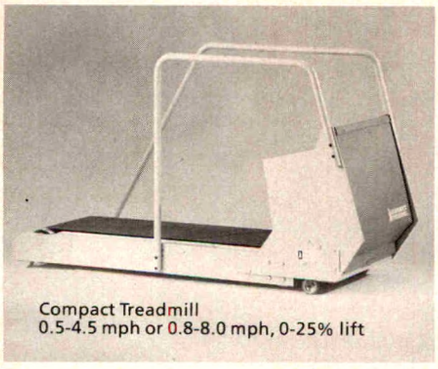

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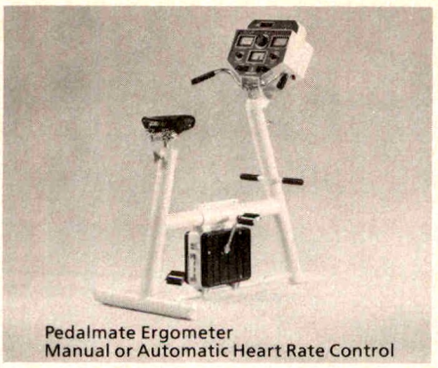

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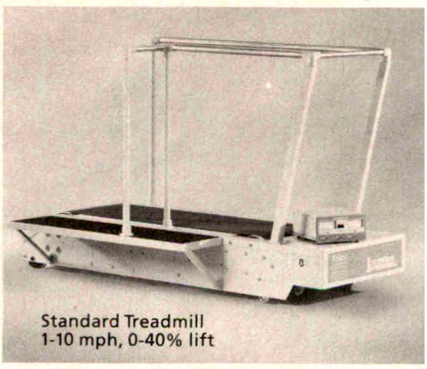

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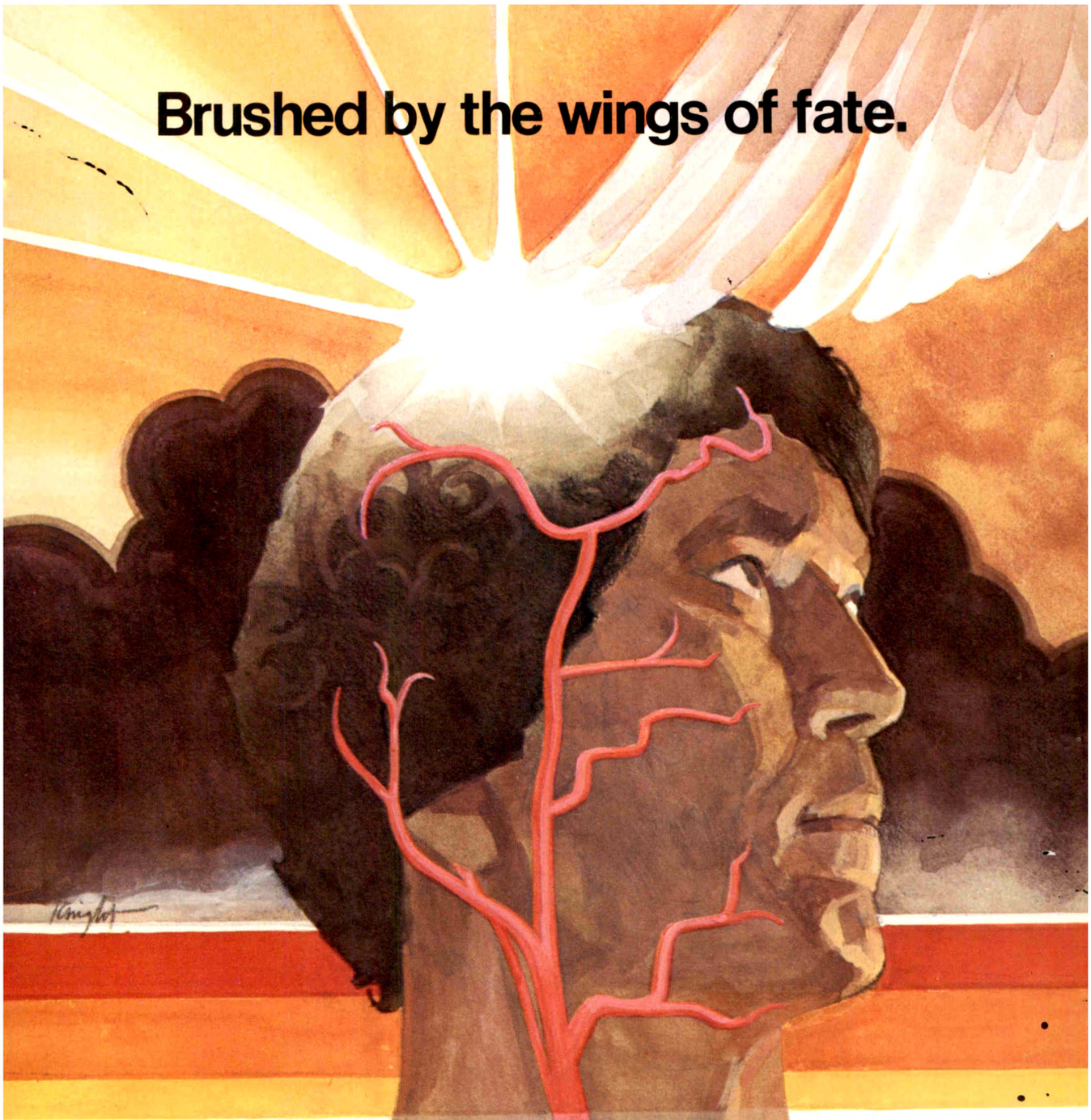

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MP80-062 A

Treatment of d-Transposition of the Great Arteries: Management of Hypoxemia After Balloon Atrial Septostomy

CATHERINE G. HENRY, MD
DAVID GOLDRING, MD, FACC
ALEXIS F. HARTMANN, MD, FACC
CLARENCE S. WELDON, MD, FACC
ARNOLD W. STRAUSS, MD

St. Louis, Missouri

Between 1975 and 1979, a group of 43 patients with d-transposition of the great arteries were diagnosed and underwent Rashkind balloon atrial septostomy at the time of initial catheterization. Thirty-six (88 percent) survived to the time of intraatrial baffle repair, and 31 (72 percent) are long-term survivors, 2 of them now awaiting repair. Palliative operations were performed in nine patients before definitive surgery; four of these patients are long-term survivors. Prostaglandin E_1 infusion improved oxygenation and relieved acidosis in four patients. It is concluded that most patients with d-transposition of the great arteries will survive to elective intraatrial baffle repair between 6 and 12 months without surgical palliation in spite of significant hypoxemia. Prostaglandin E_1 infusion may be life-saving and provide sufficient palliation in patients with persistent hypoxemia and acidosis after balloon atrial septostomy.

Since the introduction of the Rashkind balloon atrial septostomy in 1966[1] for management of infants with d-transposition of the great arteries in the neonatal period, early mortality has been reduced from about 50 percent in the 1st month of life before 1966,[2,3] to 10 to 15 percent since then.[4,5] Early deaths after balloon atrial septostomy have been due to congestive heart failure, sepsis, complications of balloon atrial septostomy, neurologic and renal problems and persistent hypoxemia.[3] Although balloon septostomy results in a marked increase in oxygen saturation immediately after the procedure in most cases,[7–9] significant hypoxemia often recurs even after creation of a sizable atrial septal defect.[10]

Opinion has varied about management of these persistently hypoxemic infants in the early period after atrial septostomy. Blalock-Hanlon septectomy is performed at some centers,[11–13] but the mortality rate of surgical septectomy is 20 to 25 percent[14,15] and the operation is often ineffective in relieving arterial desaturation.[3,16]

Recently, prostaglandin E_1, a potent dilator of the ductus arteriosus in the early neonatal period, has been noted to cause a significant rise in oxygenation in patients with transposition of the great arteries having persistent hypoxemia after balloon septostomy.[12,16–19] However, the effect has been transient in most cases, and subsequent management of these recurrently hypoxemic patients has varied. Some centers prefer to postpone definitive repair until the infant is at least 1 year old, performing intermediate palliation if indicated,[20,21] but most have recommended elective intraatrial baffle repair at age 1 year or earlier.[10,22–] More recently, primary repair in infants as young as 4 days of age with persistent hypoxemia after balloon septostomy has been performed with a high survival rate and small incidence of morbidity.[13,27,28]

In this paper we review our experience from 1975 to 1979 with patients with transposition of the great arteries and suggest guidelines for early management of patients with hypoxemia who have no significant obligatory shunt (ventricular septal defect or patent ductus arteriosus). We have found that the majority of patients without any obligato

From the Washington University School of Medicine, Edward Mallinckrodt Department of Pediatrics, Division of Cardiology, St. Louis Children's Hospital, St. Louis, Missouri. This study was aided in part by the Alpha Phi Fund, St. Louis, Missouri. Manuscript received July 28, 1980, accepted September 9, 1980.

Address for reprints: Catherine G. Henry, MD, St. Louis Children's Hospital, 500 South Kingshighway, St. Louis, Missouri 63110.

shunt will have an arterial oxygen pressure level of less than 30 torr (oxygen saturation less than 60 percent) after creation of an adequately sized atrial septal defect by balloon septostomy, yet will survive to undergo elective intraatrial baffle repair between 6 and 12 months of age without a surgical palliative procedure. A subgroup of these patients will have hypoxemia and acidosis after balloon septostomy. We have used prostaglandin E_1 to treat four of these patients,[29] and all had subsequent improvement in oxygen and resolution of acidosis.

Methods

Patients: Between January 1, 1975 and December 31, 1979, 43 infants (36 male, 7 female) admitted to St. Louis Children's Hospital were found to have d-transposition of the great arteries on cardiac catheterization. The age at initial catheterization ranged from several hours to 5 months; 33 infants (77 percent) were studied in the 1st week of life (Fig. 1). Patients with valve atresia, univentricular heart or significant coarctation of the aorta were not included. A moderate to large shunt was demonstrated angiographically in 22 patients whose predominant lesion was a ventricular septal defect (12 patients) or a patent ductus arteriosus (10 patients). An additional seven patients had angiographic evidence of a small (less than 2 mm diameter) patent ductus arteriosus, and three patients had a small (less than 2 mm diameter), hemodynamically insignificant ventricular septal defect. Significant subpulmonary stenosis was demonstrated angiographically in one patient with intact ventricular septum on initial catheterization.

All patients underwent Rashkind balloon septostomy at the time of initial catheterization; a 3 to 4 ml (5 French Edwards) balloon was used in all cases except one, in whom a 1.5 ml (4 French) balloon was used because of the patient's small size (1,800 g).

Prostaglandin E_1 infusion: Four patients with marked hypoxemia and acidosis after Rashkind balloon septostomy received prostaglandin E_1 (Upjohn) infusion through an umbilical artery catheter with the tip at the level of fifth or sixth thoracic vertebra. Criteria for beginning prostaglandin E_1 infusions were (1) reduction in PaO_2 to 20 to 25 torr after balloon septostomy, and (2) concomitant acidosis (pH less than 7.35).

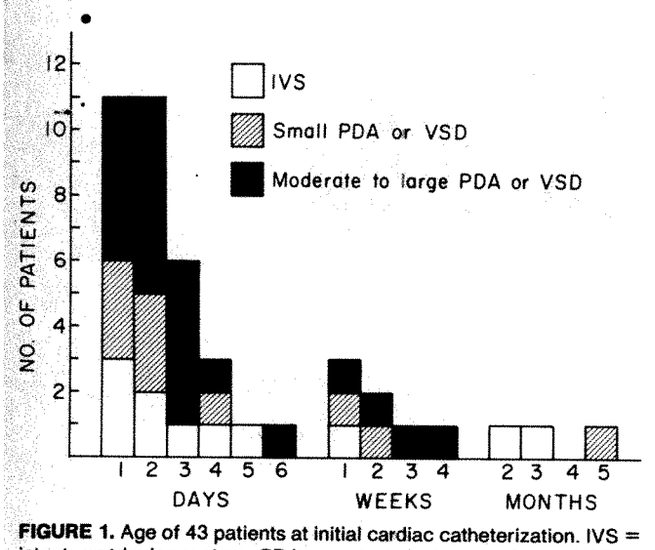

FIGURE 1. Age of 43 patients at initial cardiac catheterization. IVS = intact ventricular system; PDA = patent ductus arteriosus; VSD = ventricular septal defect.

Surgical therapy: Patients with a large ventricular septal defect at the time of initial catheterization underwent recatheterization at age 6 months, and those with an intact ventricular septum were recatheterized at age 6 to 12 months. Symptomatic patients underwent recatheterization before surgical palliation or early repair. The time of repair ranged from 3 months to 2 5/12 years, most elective repairs (25 of 36 patients with repair to date) being performed between 10 and 14 months of age. Early repair (3 to 10 1/2 months) was performed because of hypoxemia (four patients), marked growth failure (three patients) or cerebrovascular accident (one patient). The Mustard intraatrial baffle repair was performed in the initial 23 patients, of whom 13 had simple transposition with an intact ventricular septum and 10 had a previous palliative procedure requiring dismantling or additional anomalies, or both. Modified Senning procedures[31] were performed in the subsequent 13 patients, of whom 10 had simple transposition with an intact ventricular septum and 3 had additional associated lesions.

Results

Results of balloon atrial septostomy (Table I): Patients with a moderate to large patent ductus arteriosus or ventricular septal defect presented with a higher PaO_2 than did those with an intact ventricular septum or a small shunt. Rashkind septostomy resulted in substantial initial improvement in systemic oxygen saturation (10 to 62 percent) in all but five patients. Patients with a small ventricular septal defect responded to septostomy with a rise in PaO_2 similar to that of infants with an intact ventricular septum. Patients with a moderate to large ventricular septal defect or a patent ductus of any size had significantly greater increase in initial PaO_2 levels than did patients with an intact ventricular septum or a hemodynamically insignificant ventricular septal defect. Oxygen saturation after septostomy decreased to fairly stable levels within a few hours of the procedure and were not notably different from values before septostomy except in patients with a persistently patent ductus arteriosus, who had a sustained rise in oxygenation after septostomy. As compared with patients who had shunts, patients with an intact ventricular septum had substantially lower PaO_2 values after septostomy—less than 30 torr in all and less than 20 torr in five (50 percent of patients with an intact ventricular septum). An additional four of seven patients with a small patent ductus at initial catheterization had a PaO_2 less than 20 torr within 48 hours of balloon atrial septostomy, presumably secondary to ductal closure. Thus, patients with a patent ductus arteriosus in the early period after Rashkind septostomy had a significantly higher oxygen saturation than that of patients having only an intact ventricular septum. Indeed, the presence of a sizeable ventricular septal defect or patent ductus arteriosus was essential to maintain oxygen saturation above 60 percent in the early period after septostomy.

All but one patient with intact ventricular septum or small ventricular septal defect had PaO_2 less than 30 torr at the time of hospital discharge 2 to 14 days after

TABLE I

Results of Balloon Atrial Septostomy [mean ± standard error of the mean (range)]

Angiocardiographic Diagnosis	Patient (n)	PaO_2 (torr) Admission	PaO_2 (torr) Within 2 Hours	PaO_2 (torr) Lowest Representative Value Within 48 hours of Septostomy	Oxygen Saturation at Follow-up Catheterization (%)
TGA with IVS*	10	20.1 ± 1.5 (13–29)	34.1 ± 1.5 (29–43)	20.7 ± 1.2 (17–27)	73.9 ± 1.9 (65–84)
TGA with small PDA	7	20.5 ± 2.0 (15–27)	41.4 ± 2.9 (32–52)	22.6 ± 5.0 (17–30)	58.4 ± 9.9 (32–80)
TGA with moderate to large PDA	10	29.0 ± 2.2 (17–38)	48.3 ± 2.8 (33–58)	35.4 ± 1.7 (29–48)	69.2 ± 2.4 (54–78)
TGA with small VSD	3	21.0 ± 4.4 (13–28)	33.0 ± 2.1 (30–37)	24.7 ± 2.3 (21–29)	—
TGA with moderate to large VSD	12	31.2 ± 2.3 (23–45)	45.2 ± 3.0 (32–63)	33.5 ± 2.1 (24–48)	71.2 ± 2.9 (52–81)

* One patient with E. coli meningoencephalitis and profound acidosis at time of catheterization was excluded from this group.
IVS = intact ventricular septum; PDA = patent ductus arteriosus; TGA = transposition of the great arteries; VSD = ventricular septal defect.

balloon septostomy (data not shown). The one exception was the patient with significant subpulmonary stenosis on initial catheterization who underwent Blalock-Taussig shunt at age 5 days with a resultant increase in PaO_2 to a mean of 36 torr. All other patients with intact ventricular septum were doing well at the time of discharge in spite of low oxygen saturation. Furthermore, all had oxygen saturation greater than 60 percent at the time of elective catheterization before definitive surgery (Table I). Two patients with an intact ventricular septum and a small patent ductus arteriosus at initial catheterization had satisfactory oxygenation at time of initial hospital discharge but required early operative intervention (at age 1 and 9 months, respectively) because of increasing cyanosis. The other patients in this group had satisfactory oxygenation at later elective catheterization. Thus, initial hypoxemia occurring after balloon septostomy in patients with intact ventricular septum was well tolerated and oxygenation increased to satisfactory levels without need for additional surgical intervention. There were no early deaths that could be attributed directly to the procedure and no early or late deaths because of an inadequate atrial septostomy.

As a further measure of the adequacy of balloon septostomy, the size of the atrial septal defect was assessed at the time of operation or postmortem examination. The atrial septal defect was large (1.5 to 2.5 cm) in 27, moderate (1 to 1.5 cm) in 4 and small (less than 1 cm) in 4. Of the four patients with a small atrial septal defect noted at operation, two had undergone repeat catheterization 24 hours and 2 weeks after the initial balloon septostomy procedure because of marked hypoxemia (PaO_2 less than 20 torr). A widely patent atrial septal defect was demonstrated angiographically and by pressure data in both patients. The other two patients had satisfactory oxygenation (PaO_2 30 to 50 torr) during the 1st week after septostomy. Furthermore, persistent hypoxemia after septostomy occurred frequently in patients who had an anatomically documented large atrial septal defect. Thus, there was no correlation between the size of an atrial septal defect a later surgical repair or autopsy and level of oxygenatio in the period immediately after septostomy.

Results of surgical palliation (Table II): Nin patients (21 percent) underwent a palliative surgica procedure. In 1975 three patients with severe hypox emia had a Blalock-Hanlon septectomy performec Because of poor results with this procedure (two deaths and our realization that hypoxemia was usually not du

TABLE II

Results of Palliative Surgical Procedures

Procedure	Associated Defect	Age	Outcome
BH	—	5 days	PaO_2 decreased to 17, 48 hours after septostomy; died of low output failure after aortopulmonary shunt
BH	—	3 mo	Improved oxygenation; survived t elective repair at 24 months
BH	—	5 mo	Died within 24 hours with pulmonary vascular congestion and intraalveolar hemorrhage
BT	SPS	3 days	Improved oxygenation; survived t elective repair at 14 months
BT	—	7 days	Improved; died 3 months later of aspiration secondary to diaphragmatic paralysis
BT	SPS	32 days	No improvement; shunt nonfunctional and had paralysis of right hemidiaphragm; successful repair at 7 months but died with baffle obstruction
BT	—	8 days	No improvement; functioning shunt documented; survived elective repair
BT	SPS	6 1/2 mo	Improved; survived elective repa at 2 5/12 years
PA band	Large supracristal VSD;severe TI	6 days	Initial improvement in congestiv heart failure; died at attempted repair at 10 1/2 months

BH = Blalock-Hanlon; BT = Blalock-Taussig; PA = pulmonary arte SPS = subpulmonary stenosis; TI = tricuspid insufficiency; VSD ventricular septal defect.

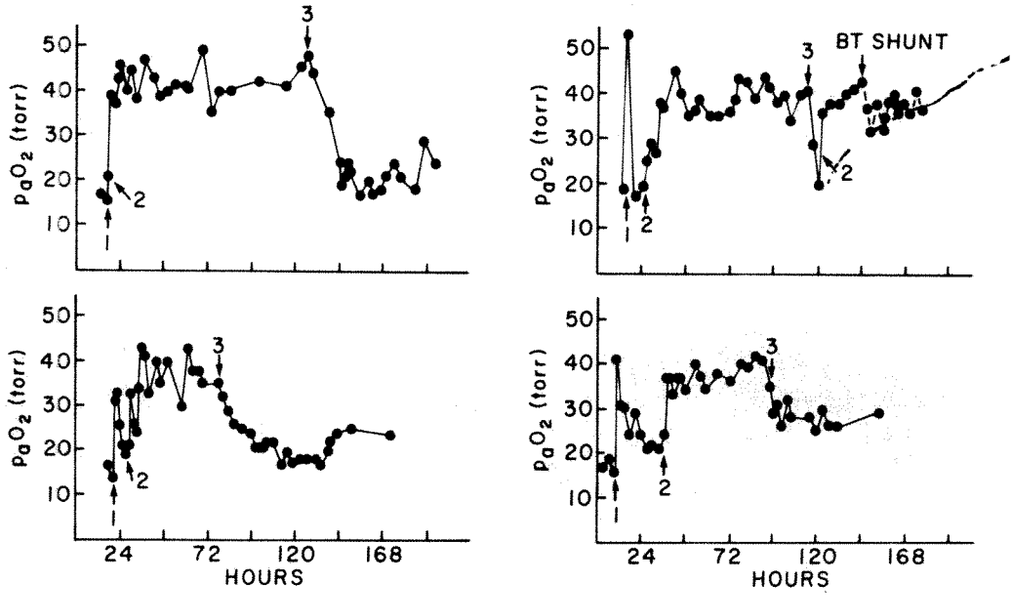

FIGURE 2. Results of prostaglandin E_1 infusions. Times are indicated for balloon atrial septostomy (1), commencement of prostaglandin E_1 infusions (2) and discontinuation of prostaglandin E_1 infusions (3). BT shunt = Blalock-Taussig shunt procedure.

to a small atrial septal defect (see preceding), this procedure has not been used since 1975.

Instead, we provided palliation for hypoxemia in five patients with a Blalock-Taussig shunt. In three of these, decreased pulmonary blood flow secondary to subpulmonary stenosis was the cause of the hypoxemia.[32] In the other two, a Blalock-Taussig shunt was performed in the absence of subpulmonary stenosis. One of these patients, who previously had demonstrated increased oxygenation during prostaglandin E_1 infusion, was also improved following the shunt procedure (Fig. 2). Although no operative mortality occurred, two patients had significant morbidity from paralysis of the right hemidiaphragm and one shunt was nonfunctional.

Results of palliation with prostaglandin E_1 infusion: Four patients were treated with prostaglandin E_1 because of hypoxemia (PaO_2 16 to 21 torr) and acidosis (pH less than 7.35) after adequate balloon septostomy (Fig. 2). Dilatation of the ductus arteriosus occurred in all, including one patient who had a closed ductus at the time of initial angiography (Fig. 3). Prostaglandin E_1 infusions resulted in a nearly maximal rise in PaO_2 within 15 minutes in two patients but took 2 hours for notable rises and 7 hours for maximal rises

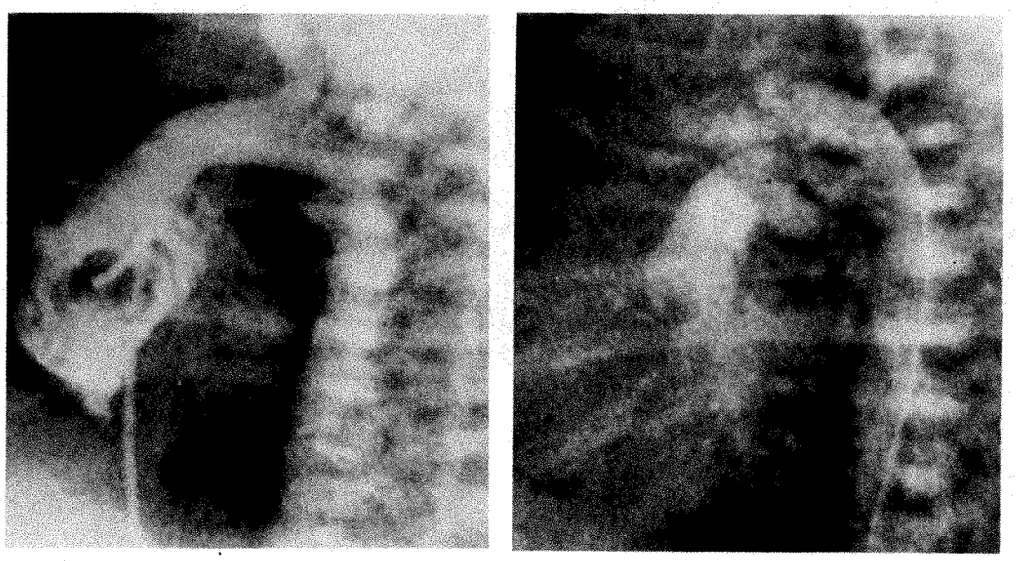

FIGURE 3. Ductal dilatation by prostaglandin E_1 demonstrated on angiography. **Left,** right ventricular injection (left anterior oblique projection) at the time of initial catheterization demonstrates ductus infundibulum with closed ductus arteriosus. **Right,** aortogram (left anterior oblique projection) during prostaglandin E_1 infusion demonstrates widely patent ductus arteriosus 15 hours later.

in the other two. During infusion, PaO_2 rose to 30 to 40 torr and acidosis was relieved in all patients. Total duration of prostaglandin E_1 infusions ranged from 50 to 108 hours. Discontinuation of the drug resulted in a reduction in PaO_2 to preinfusion levels in all patients with gradual improvement to mid-high 20 torr level by the time of discharge. In an effort to simulate the beneficial effect of prostaglandin E_1 infusion, one patient underwent a successful Blalock-Taussig shunt. The other three patients tolerated hypoxemia without further development of significant acidosis, and they subsequently underwent successful definitive repair electively at age 10 to 12 months.

Mortality and results of corrective surgery (Table III): Five patients died before definitive repair. One patient died a few hours after initial catheterization with E. coli meningoencephalitis and another patient with a large ventricular septal defect had fatal congestive heart failure and renal failure at age 6 months. Three deaths followed palliative surgery.

In addition, there were seven deaths at the time of or subsequent to definitive repair (Tables III and IV). Three patients were unable to regain adequate cardiac function without cardiopulmonary bypass. A fourth patient, who had undergone pulmonary arterial banding in the 1st week of life, died of low output secondary to tricuspid insufficiency after repair. Another patient with a patent ductus arteriosus and congestive heart failure survived repair at 7 months of age but died one month later of respiratory failure. Two patients survived initial repair but died during a subsequent surgical attempt to relieve baffle obstruction of systemic or pulmonary venous return. No late deaths due to arrhythmias or sudden deaths have occurred.

Thus, of our 43 patients, 31 (72 percent) are living, including 29 patients who have had intraatrial baffle repair and have been followed up for 2 months to 4 1/2 years, and 2 patients who are awaiting surgical repair. Thirty-six (88 percent) of 41 patients survived to definitive repair at age 7 months to 2 5/12 years; only two deaths (5 percent) occurred in those patients who underwent balloon septostomy without further palliation. Mortality was substantially greater in those patients who underwent surgical palliation before definitive repair. Of the nine patients who had surgical palliation, only four are long-term survivors.

Discussion

Factors contributing to improved survival: Survival of infants with transposition of the great arteries has been improved dramatically since the introduction of the Blalock-Hanlon septectomy, balloon atrial septostomy and the venous transposition operations described by Mustard and Senning. With current management, deaths in the 1st month of life (10 to 15 percent)[6] have contributed significantly to overall mortality. In contrast, only three of our patients (7 percent) died in the first 5 months of life. We believe that early referral of our patients (Fig. 1) was one important factor in their survival since few were severely acidotic at time of admission (16 percent with pH less than 7.25). Improved survival of infants with transposition concomitant with earlier referral to centers equipped to perform emergency balloon septostomy was also noted in a recent survey.[15]

Second, performance of a technically adequate balloon septostomy contributed to the high rate of early survival in our patients. Although others have reported mortality due to complications of balloon septostomy,[33–35] at our institution this procedure has not been associated with any deaths in the last 5 years.

A third factor that contributed to excellent early survival was conservative medical management without further surgical palliation in patients whose early

TABLE III

Mortality in 43 Patients

	Diagnosis at Initial Cardiac Catheterization		
	IVS or Small Shunt n = (21)	Moderate to Large Shunt n = (22)*	Total
Death before definitive repair			
Early medical	1		
After palliative surgery	2†,†		
Awaiting definitive repair	1†	1	
Total	4	1	12%
Operative death, intraatrial baffle repair‡	3	1†	11%
Late death	1†	2	
Total	8	4	28%

* Of the 22 patients with a moderate to large shunt at initial cardiac catheterization, only three had moderate to large shunts documented at follow-up preoperative catheterization. Seven patients had only small residual shunts. Only one of three patients with moderate to large shunts preoperatively is a long-term survivor. †Patients who had a palliative surgical procedure. ‡Operative mortality rate based on 36 patients who have undergone intraatrial baffle repair.

TABLE IV

Corrective Procedures in 36 Patients (1975–1979)

Procedure	Patients (n)	Mortality	
		Operative	Late
Mustard			
Simple	13	1	1
Complex*	10	1	2
Total	23	2 (9%)	3 (13%)
Senning			
Simple	10	1	
Complex†	3	1	
Total	13	2 (15%)	0 (0%)
Series total		4 (11%)	3 (8%)

*Includes two patients with ligation of a patent ductus arteriosus (one operative and one late death), two with ligation of a Blalock-Taussig shunt (one late death), two with closure of ventricular septal defect and resection of left ventricular outflow tract obstruction, one with closure of a ventricular septal defect, one with resection of left ventricular outflow tract obstruction, one with closure of a ventricular septal defect and pulmonary valvotomy, and one with ligation of a Blalock-Taussig shunt and resection of left ventricular outflow tract obstruction. †Included one patient with closure of a ventricular septal defect and resection of left ventricular outflow tract obstruction, one with ligation of a patent ductus arteriosus and one with repair of tricuspid valve, debanding of pulmonary artery, angioplastic reconstruction of pulmonary artery and closure of a ventricular septal defect (operative death).

post-septostomy oxygen saturations were "unsatisfactory" as defined in the past. Satisfactory early improvement after balloon septostomy has been previously defined as either an increase in oxygen saturation of greater than 10 percent with reduction in interatrial mean pressure gradient to less than 2 mm[20,35] or arterial saturation of greater than 50–75 percent.[11–14,20] Satisfactory late improvement has been defined as survival to six months with oxygen saturation at 60 percent or higher.[20,22,36] At other institutions, Blalock-Hanlon septectomy has been the most frequent form of palliation in infants who have not improved significantly after balloon atrial septostomy. However, this operation carries a 20 to 25 percent mortality rate.[14,15] In our series, the only deaths in patients with an oxygen saturation of less than 60 percent (PaO_2 less than 30 torr) after balloon septostomy occurred in those who underwent palliative procedures (Table III). Indeed, although most patients with an intact ventricular septum or small ventricular septal defect or patent ductus arteriosus were transiently hypoxemic early after balloon septostomy, none of our 21 patients in these groups who were managed medically died in the neonatal period, except one with E. coli meningoencephalitis. Early hypoxemia resolved over time and remained at satisfactory levels in all but five patients (three with left ventricular outflow obstruction). Thus, we believe that hypoxemia alone is not a sufficient indication for surgical septectomy early after technically adequate balloon septostomy.

Surgical septectomy is often ineffective in relieving arterial desaturation[3,16] and does not guarantee permanent presence of an atrial septal defect because subsequent spontaneous closures have been noted on occasion.[14] Thus, the only cases in which Blalock-Hanlon septectomy might be indicated in the immediate period after balloon septostomy would be those in whom atrial septal defect size is determined to be inadequate by two-dimensional echocardiography[16] or a repeated catheterization. Indeed, subjection of a markedly hypoxemic infant to Blalock-Hanlon septectomy may be an unnecessary stress, and might account for some avoidable mortality.

Prostaglandin E_1 infusion: A fourth factor that contributed to the high rate of early survival in our patients was use of prostaglandin E_1 infusion in four hypoxemic newborns with associated acidosis (pH less than 7.35) after balloon septostomy. Acidosis and hypoxemia were relieved in all four. Previous authors have described use of prostaglandin E_1 in patients with transposition with variable success. Of the 18 patients with transposition and intact ventricular septum treated with prostaglandin E_1 and reported on to date,[12,16–19] all but four showed an increase in oxygen saturation. Successful ductal dilatation by prostaglandin E_1 has been accomplished as late as 28 days of age,[37] but it is less likely to occur after the first week of life.

In our patients, as well as those reported on previously,[12,17–19] discontinuation of prostaglandin E_1 infusion resulted in return of oxygen saturation to preinfusion levels, implying ductal closure. However, acidosis did not recur despite low oxygen saturation. Rather, a brief period (2 to 4 days) of prostaglandin E_1 infusion served to relieve acidosis secondary to hypoxemia present on admission or subsequent to the stress of cardiac catheterization, angiocardiography and balloon septostomy. The patients were then able to tolerate hypoxemia without the development of further metabolic acidosis.

Blalock-Taussig shunt: Relief of persistent or recurrent hypoxemia and acidosis after balloon septostomy with prostaglandin E_1 infusion may be the only palliation necessary in patients without significant left ventricular outflow tract obstruction. However, if acidosis recurs with discontinuation of prostaglandin E_1, a Blalock-Taussig shunt will improve oxygenation by simulating the hemodynamics of a patent ductus arteriosus (Fig. 2). Although palliation of transposition by aortopulmonary anastomosis has been suggested before,[18,38] it is currently not accepted as standard treatment except in patients with pulmonary stenosis.[3,11,21,39] Indeed, most reported attempts to create aortopulmonary anastomoses in neonatal transposition have resulted in congestive heart failure[40] and a high mortality rate (approximately 75 percent).[15] Our experience with the Blalock-Taussig shunt in transposition (Table II) is limited; however, no operative deaths occurred and the shunt generally improved oxygenation. Furthermore, because of the small size of the shunt, there was no instance of congestive heart failure and four of the five patients who had a Blalock-Taussig shunt survived to successful intraatrial baffle repair. We believe that a Blalock-Taussig shunt may be an acceptable palliative procedure in infants with transposition and subpulmonary stenosis[32] or in neonates with transposition and persistent acidosis who have demonstrated a positive response to prostaglandin E_1.

Indications for early definitive surgical repair: Some controversy has recently arisen concerning the optimal age for repair in patients with transposition of the great arteries. Early definitive repair has been advocated by several workers,[23,26,27,40,41] but the mortality rate in infants less than 2 months old is high in some series.[15,22] However, in the most recent series[13,27,31,42] operative mortality rates have been low (0 to 7 percent) in patients treated with definitive repair, even in the neonatal period, without intervening palliative procedures. Persistent hypoxemia after technically adequate balloon septostomy was the reason given most often for early reparative intervention. However, hypoxemia alone may be well tolerated without need for early operative intervention. We found that 88 percent of our patients survived to definitive repair (average age 11.6 months) with an operative mortality of 11 percent. These results compare favorably with those of other recent series which report a 19 to 27 percent mortality rate before repair[3,6,20,35,39] and an 11 to 26 percent mortality rate at definitive operation.[3,6,10,15,20,22,23,41] Thus, we feel justified in waiting to perform elective repairs at ages 6 to 10 months with the hope that ventricular septal defects will close in some patients and

that venous obstructive complications of intra-atrial baffle repairs may be avoided in older patients.

Guidelines for early management: As a consequence of our findings, we suggest the following guidelines for early management of patients with transposition of the great arteries: (1) balloon atrial septostomy and conservative medical management for all patients without acidosis regardless of oxygen saturation following Rashkind septostomy, (2) prostaglandin E_1 infusion for 2 to 5 days in those patients with persistent acidosis after balloon septostomy with more prolonged infusion if significant acidosis recurs after discontinuation of the drugs,[19] and (3) early Senning or Mustard intraatrial baffle repair in any patient over one month of age with growth failure, uncontrolled congestive heart failure or increasing cyanosis caused by catheterization-proven subpulmonic stenosis, increasing pulmonary vascular resistance or inadequate atrial septal defect. Blalock-Taussig shunt may be considered as an alternative in patients with subpulmonic stenosis or persistent hypoxemia in the first 1 to 2 months of life. Use of these guidelines may further improve the overall prognosis above the 72 percent late postoperative survival which we have already achieved.

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Addendum

Since the preparation of this report, the two remaining patients awaiting definitive repair have undergone a successful Senning operation.

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Results of Intraventricular Baffle Procedure for Ventricular Septal Defect and Double Outlet Right Ventricle or d-Transposition of the Great Arteries

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Thirty patients with ventricular septal defect and d-transposition of the great arteries or double outlet right ventricle underwent placement of an intraventricular baffle to achieve physiologic correction. Eighteen of these patients also required an external conduit to establish continuity between the right ventricle and the pulmonary artery. There was an overall 22 percent early mortality rate, although the rate was 63 percent in patients who weighed less than 10 kg. There was an additional 20 percent late mortality rate, primarily related to conduction disturbances and pulmonary vascular obstructive disease, problems that have not occurred in patients operated on since 1974. Of the survivors, all are asymptomatic and as a group have achieved a significant weight gain. Many have residual hemodynamic abnormalities that required cardiac catheterization for precise assessment. Four patients have been reoperated on, with no additional mortality.

With advances in surgical technique, a wide variety of complicated forms of congenital cardiac defects have been treated by cardiovascular surgeons. Previous reports have described an intraventricular baffle procedure performed in patients with d-transposition of the great arteries and ventricular septal defect[1–6] and patients with double outlet right ventricle and ventricular septal defect[5–10] to achieve physiologic correction of the circulation. When this procedure is employed, all patients with d-transposition of the great arteries and ventricular septal defect[1–6] require interposition of an external conduit between the body of the right ventricle and the pulmonary artery. Patients with double outlet right ventricle and ventricular septal defect who have anomalies of the pulmonary or coronary arteries also require an external conduit.[5,6] Previous reports have described the surgical technique and operative mortality[1–10] or selected hemodynamic findings[4–6,11,12]; in this report, we describe comprehensive long-term follow-up findings in 30 patients who underwent an intraventricular baffle procedure.

Methods

Patient groups: Between March 1970 and March 1978, a total of 14 patients with d-transposition of the great arteries and ventricular septal defect (Group I) and 16 patients with double outlet right ventricle and ventricular septal defect (Group II) underwent intracardiac repair at this institution. Complete diagnosis and previous surgical procedures for each patient are listed in Table I. In all patients, two ventricles communicated through a ventricular septal defect, and the aorta arose from the right ventricle. In Group I the pulmonary artery arose from the left ventricle. In Group II, both the aorta and the pulmonary artery arose from the right ventricle: in 11 patients the ventricular septal defect was subaortic, and in 5 the defect was subpulmonary.

Surgical procedure: With use of cardiopulmonary bypass, a knitted Teflon patch was fashioned inside the right ventricle so that left ventricular blood was ejected through the ventricular septal defect, remained on the left side of the baffle and was directed out the aortic root. Right ventricular outflow was managed as follows: (1) In 18 patients—all 14 patients in Group I and 4 patients in

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TABLE I

Summary of Data in 30 Cases

Case & Sex	Date of Birth (mo/yr)	Additional Diagnoses	Surgery: Age (yr)	Surgery: Sys. O_2 Sat. (%)	Surgery: Hct	Surgery: Wt (kg)	Surgery: Conduit Size (mm)	Comments
Group I: d-Transposition and Ventricular Septal Defect								
1 M	2/74	ASD	0.6	84	46	4.8	14	Died 1 day: low output
2 M	12/74	ASD	0.9	79	52	10.3	16	SBE 2 yr postop
3 F	3/73	ASD	1.0	83	43	7.0	16(u)	. . .
4 M	10/72	PS	1.5	82	51	8.0	14(u)	Died 1 day: low output
5 F	3/71	PS; BT	1.8	50	66	9.1	16(u)	. . .
6 F	3/73	PS; BT	4.0	70	63	12.2	16	. . .
7 F	6/70	PS; BT	4.2	65	56	17.4	16	. . .
8 F	10/66	PAt; BT	5.0		53	18.0	14(u)	. . .
9 F	5/68	PS; Wat; Reop:Sub AS; res VSD	6.5 9.5	72 . . .	52 . . .	16.5 23	16 Same	. . . . . .
10 F	9/68	ASD; PS; BT; Wat	7.5	84	58	20	16	Died 2 yr: PVOD
11 F	6/65	PS	11	80	64	22	20	
12 F	8/60	PS; Glenn	17	75	70	58	25	Died 3 mo: Candida endocarditis
13 M	8/44	PS	28	78	75	64	25	
14 M	5/35	PS	37	70	59	65	25	Postop atrial flutter; PVCs
Group II: Double Outlet Right Ventricle								
15 M	3/75	TB	0.8	87	60	4.8	16	Died 2 wk: decerebrate
16 M	6/74	Inf, sup PS	1.3	68	42	7.0		Died 1 day: low output
17 M	11/74	PAB. Reop: Sub AS, LV-RA	1.4 2.5	77 92	45 38	8.0 11.0		Postop CHF
18 M	9/70		1.9		34	10.1		
19 F	2/76	TB,PAB, Inf PS	2.1		55	8.3		Died 1 day: low output
20 M	8/71	Inf, sup PS. Reop: conduit obstruction	3.6 7.3	75	55 19.0	12.5 20	16	
21 F	9/65	Inf PS	4.7	82	44	14.8		CHB; died 6 mo
22 F	8/69	PAB	5.5	91	45	19.0		
23 M	8/67	Dex, PAB, TB	5.7	69	55	15.0		CHB; died 2 yr
24 F	9/62	Inf, sup PS, Potts	7.5	78	43	15.4		Died 7 yr: PVOD
25 M	11/65	TB, PS	7.8	80	70	20	16	Transient CHB, now 2:1 A-V block
26 F	9/59	Inf PS, BT, pulm At	10.7		46	23		
27 F	1/62	TB, PDA, inf PS	11.5	71	50	28		Died 2 wk: respiratory insufficiency
28 M	12/52	Inf PS, Potts	17		52	66		Died 2 yr: unexplained
29 M	11/53	Inf PS, ASD, LSVC. Reop: LV-RA	18 23		60	56 65		
30 M	1/26	Inf PS, PS, BT	48		58	61	25	Died 10 days: low output

ASD = atrial septal defect; A-V = atrioventricular; BT = previous subclavian-pulmonary arterial anastomosis; CHB = complete heart block, pacemaker implanted; CHF = congestive heart failure; Cond obstr = obstruction to right ventricular outflow inside external conduit, proximal to heterograft valve; Dex = dextrocardia; Hct = hematocrit; Glenn = previous superior vena cava–right pulmonary arterial anastomosis; Inf PS = infundibular pulmonary stenosis; LSVC = persistent left superior vena cava; LV-RA = residual shunt from the left ventricle to the right atrium; PAB = previous pulmonary arterial band; PDA = patent ductus arteriosus; postop = postoperative; Potts = previous descending aorta–pulmonary arterial anastomosis; Pulm At = pulmonary atresia; PS = pulmonary valve stenosis; PVCs = occasional premature ventricular complexes; PVOD = pulmonary vascular obstructive disease; Reop = reoperation; Res VSD = residual ventricular septal defect (intraventricular communication); SBE = subacute bacterial endocarditis; Sub As = subaortic stenosis; sup PS = supravalvular stenosis of pulmonary arteries; Sys O_2 Sat = systemic oxygen saturation; TB = Taussig-Bing anomaly (subpulmonary ventricular septal defect); (u) = unvalved external conduit.; Wat = previous ascending aorta–right pulmonary arterial anastomosis.; Wt = body weight.

Group II—the pulmonary artery was divided and the proximal stump oversewn; a woven Dacron® conduit was interposed between the right ventriculotomy and the distal stump of the pulmonary artery. This conduit was unvalved in 4 patients treated early; in the other 14 patients a porcine aortic valve prosthesis[3] was incorporated into the Dacron conduit. (2) In the remaining 12 patients, all in Group II, an external conduit was not utilized, but 11 of these patients required infundibular resection or supravalvular pericardial patch, or both.

Surgical outcome: There are three categories of outcome: (1) early death (less than 1 month after operation), (2) late death (more than 1 month after operation), and (3) survival. To evaluate the variables that may have influenced the surgical result, surgical outcome was correlated with preoperative hematocrit, systemic arterial oxygen saturation, age, weight and performance of previous palliative procedures. Also, to investigate the effects of accumulated experience with the surgical procedures at Stanford Medical Center, the outcome in the first 15 patients were compared with the outcome in the last 15 patients. Comparisons within these groups were made using the chi-square test for statistical significance.[13]

Postoperative follow-up: Follow-up information was obtained directly from 20 patients and from the referring physician of 10 others. Of the surgical survivors, 16 patients underwent cardiac catheterization 6 months to 5 years postoperatively. To assess the effect of surgery upon growth of the survivors, body weight at the time of cardiac catheterization was expressed as the number of standard deviations from the mean value in age- and sex-matched control subjects;[14] comparison was made between the values obtained at preoperative catheterization and postoperative catheterization using the two-tailed t test.[13]

Results

Clinical profiles: Fifteen of the 30 patients were male and 15 female (Table I). Of the 14 patients in Group I, 11 had pulmonary stenosis or atresia, and 7 of these had undergone previous surgical creation of a systemic to pulmonary arterial shunt; the 3 patients without pulmonary stenosis had not had previous surgery. Among the 16 patients in Group II, pulmonary stenosis was present in 10, including 4 in whom a systemic to pulmonary arterial shunt had been performed; of the 6 patients without pulmonary stenosis, 4 had had pulmonary arterial banding and in 1 of of these, subpulmonary stenosis had developed at the time of intracardiac repair.

Early mortality (Table I): Seven patients—two in Group I and five in Group II—died in the early postoperative period: five with low output, one of respiratory insufficiency, and one with postoperative cerebral damage. There was a significant relation ($p < 0.05$) between mortality and age less than 3 years. However, there was a better correlation between early mortality and weight ($p < 0.01$): Children who weighed less than 10 kg had a 62 percent operative mortality rate compared with 9 percent in patients who weighed more than 10 kg (Fig. 1). Because size significantly influenced early mortality, when the infants who weighed less than 10 kg were excluded from consideration, neither previous operative procedures nor operative experience at Stanford with these defects influenced operative mortality. Finally, the most complex combination of defects was found in our five patients with double outlet right

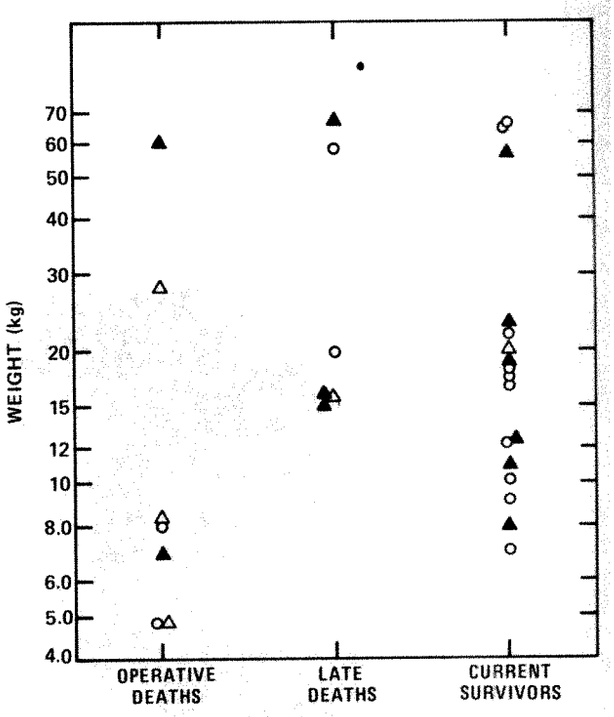

FIGURE 1. Surgical outcome in 30 patients plotted against body weight. **Open circles** = d-transposition of the great arteries and ventricular septal defect; **open triangles** = double outlet right ventricle and subpulmonary ventricular septal defect; **closed triangles** = double outlet right ventricle and subaortic ventricular septal defect.

ventricle and subpulmonary ventricular septal defect three of these five patients died early, including two who weighed less than 10 kg. Neither preoperative systemic arterial oxygen saturation nor hematocrit correlated with surgical survival.

Postoperative Evaluation

By history, all 17 current survivors are acyanotic and have improved exercise tolerance compared with that before operation. Patient 19 had findings of congestive heart failure after his first intracardiac procedure, but is now asymptomatic after reoperation. Patient 2 had Moraxellei Kingsei endocarditis, and recovered uneventfully after intravenous ampicillin therapy. Patient 12 had recurrent Candida septicemia, the cause of death 3 months after surgery.

Electrocardiographic findings, except for arrhythmias, are nonspecific, as each patient has a right bundle branch block. Patients 21, 23 and 25 had a pacemaker implanted for surgical complete heart block. Two of these patients subsequently died and, after pacemaker failure, the third has second degree heart block with 2:1 atrioventricular conduction and a ventricular rate of 75/min. Patients 10 and 13 have unifocal premature ventricular complexes at rest and Patient 10 in addition has a variety of supraventricular arrhythmias.

Chest radiographic findings are nonspecific, showing normal heart size or slight cardiac enlargement. Pulmonary vascularity appears normal in all. In patients with a valved conduit, the metallic ring associated with the heterograft valve is also seen.

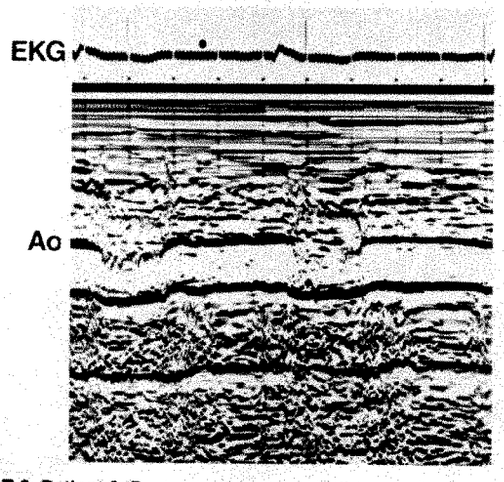

FIGURE 2. Patient 3. Postoperative echocardiogram showing systolic notching and shuddering of aortic valve. Ao = aortic root; EKG = surface electrocardiogram.

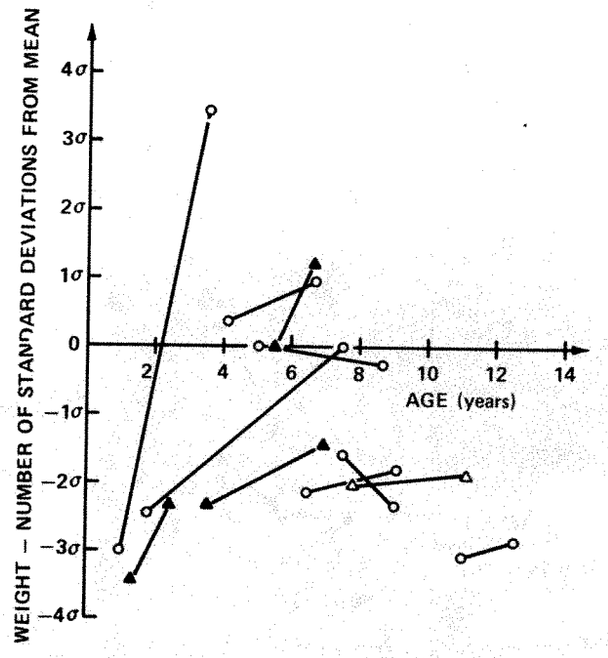

FIGURE 3. Pre- and postoperative body weights (expressed as the number of standard deviations from the mean value of age- and sex-matched control subjects) are plotted on the **vertical axis**. For each pair, the symbol at left was obtained at preoperative cardiac catheterization and the symbol at right at postoperative catheterization. Symbols as in Figure 1.

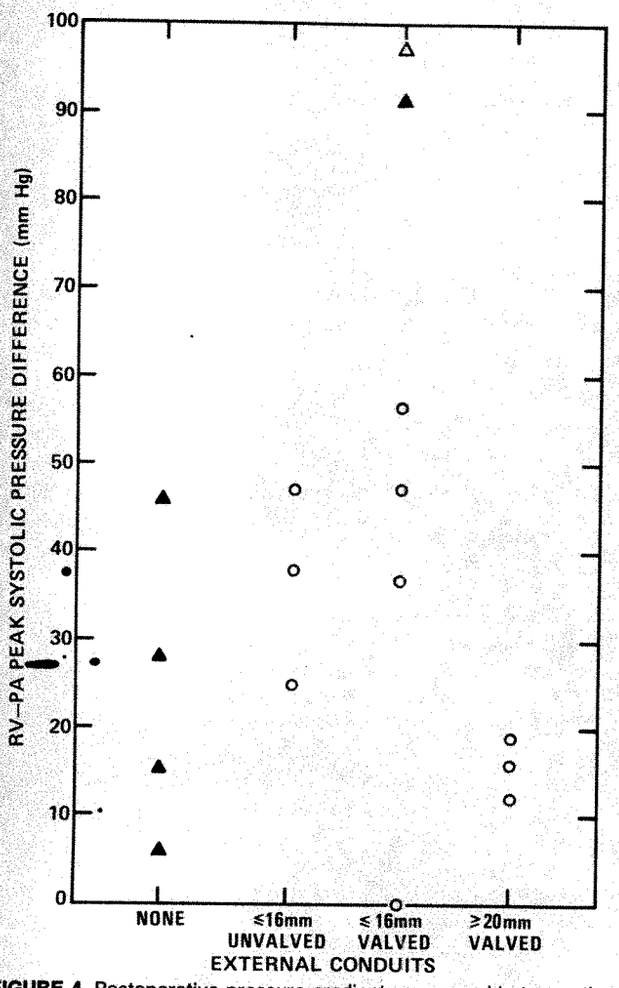

FIGURE 4. Postoperative pressure gradients measured between the body of the right ventricle (RV) and distal pulmonary artery (PA), related to type of reconstruction. Symbols as in Figure 1. None = no external conduit; ≤16 mm = 14 or 16 mm external conduit; ≥20 mm = 20 or 25 mm external conduit; VALVED = porcine heterograft valve incorporated into external conduit; UNVALVED = straight Dacron tube used as external conduit.

Echocardiography was often technically difficult in these patients, and we have been unable to image motion of the porcine heterograft valve with consistency. Notching and shudder of the aortic valve motion was often seen (Fig. 2), although this finding does not correlate with the presence of subaortic obstruction.[15]

Postoperative weight percentiles (Fig. 3), adjusted for age and sex, obtained at postoperative cardiac catheterization were significantly greater than preoperative catheterization values ($p < 0.05$); the largest gains were seen in those patients who were less than 6 years old at the time of operation.

On physical examination, all surviving patients have at least a grade 3/6 systolic murmur, and two patients with an unvalved external conduit have a diastolic murmur. The murmurs were generated by residual intracardiac defects, which can only be defined by cardiac catheterization.

Cardiac catheterization (Table II): The results can be summarized as follows:

Right ventricular outflow tract obstruction: Eight patients had a peak systolic gradient greater than 30 torr across the right ventricular outflow tract (Fig. 4). The largest gradients were found in patients in whom a 14 or 16 mm external conduit was used, and of these the conduits that contained heterograft valves were most stenotic. Obstruction was found at the junction of the right ventricle and external conduit (four patients), in the external conduit below the heterograft valve (three

TABLE II

Postoperative Cardiac Catheterization Data in 16 Cases

Case	Age (yr)	Pressures (mm Hg)				Level of Obstruction		Qp/Qs	Comments
		RV	PA	LV	Ao	RV	LV		
2	2.9	65/11	29/12	—	—	Cond-RV	—	1.0	
3	3.5	45/7	20/8	130/10	125/70	—	—	1.0	
5	7.5	62/6	15/5	90/6	85/50	Cond-RV	—	1.0	
7	6.7	67/2	11/7	120/3	77/51	Cond-RV	Baf	1.0	
8	10.4	50/4	12/2	160/8	100/70	Cond-RV	?	1.0	
9	9.1	75/10	28/10	142/14	80/60	Cond obstr	VSD*	1+	VSD
10	9.0	140/8	140/30	150/11	90/52	PVOD	VSD*	1.0	
11	12.5	30/4	17/4	140/6	120/80	—	—	1.3	VSD
13	29.	72/2	56/29	140/6	108/70	—	?	1.2	VSD
14	38.	54/10	35/13	120/5	120/80	—	—	1.0	
17	2.4	68/10	22/14	140/21	80/42	Band	Baf	1.4	LV-RA
20	7.0	105/6	14/6	90/5	85/45	Cond obstr	—	1.0	
22	6.6	54/6	27/14	114/10	110/74	Band	—	1.0	
24	10.8	75/0	60/30	100/0	100/70	PVOD	—	1+	VSD
25	11.1	110/6	13/5	160/6	90/45	Cond obstr	Baf	1.0	
29	23.	20/12	14/4	93/6	92/58	—	—	1.7	LV-RA

Ao = aortic; Baf = obstruction to left ventricular outflow at a region inside the intraventricular baffle; Band = obstruction to right ventricular outflow at site of previously placed pulmonary band; Cond-RV = obstruction to right ventricular outflow at junction of external conduit and right ventricle; PA = pulmonary arterial; Qp/QS = pulmonary/systemic flow ratio; RV = right ventricular; VSD* = obstruction to left ventricular outflow at the site of the natural ventricular septal defect. Other abbreviations as in Table I.

patients) (Figure 5) and at the point of a previous pulmonary arterial band (one patient).

Left ventricular outflow tract obstruction: Seven patients had a peak systolic gradient of 30 mm or more across the left ventricular outflow tract (Fig. 6). Although the trend was not statistically significant, small patients tended to have a larger gradient. At cardiac catheterization, the obstruction was in the intraventricular baffle in three patients (Fig. 7), at the site of the patient's natural ventricular septal defect in two and was not well localized in two.

Residual shunts: Six patients had a residual left to right shunt related to the intraventricular baffle. In four patients, the shunt was from the left to the right ventricle, and the communication was behind the septal leaflet of the tricuspid valve. In two others, the shunt was from the left ventricle to the right atrium. In all cases, pulmonary flow was less than twice systemic flow, and in two patients, the residual shunt was detected only on angiography (Fig. 7).

Pulmonary vascular obstructive disease: The highest pulmonary arterial pressures were found in two patients (Cases 10 and 24) who had previously had a surgically created aortic to pulmonary arterial shunt; the next highest pressures were found in two patients (Cases 13 and 14) who were operated on as adults. Mean pulmonary arterial pressure was at the upper limits of normal in four other patients, one of whom had a residual intracardiac shunt at postoperative cardiac catheterization.

Reoperation

Only Patient 17 was symptomatic after operation; this patient and three others (Patients 9, 20 and 29) were reoperated on and all did well after reoperation. Reoperation included closure of a residual left to right shunt (Patient 29), closure of a residual shunt and enlargement of the left ventricular outflow tract by removing a portion of the rim of the native ventricular septal defect (Patients 9 and 17) or replacement of the valved external conduit (Patient 20). In the latter patient, the conduit was replaced with a 20 mm valved conduit 3.7 years after the original implantation. The leaflets of the replaced valve were in excellent condition and the valve appeared to be competent; however, below the valve, a very exuberant fibrous reaction severely compromised flow into the conduit (Fig. 5). The porcine valve in Patient 9 was also visualized from above at the time of reoperation, and appeared to be in excellent condition. Reoperation was suggested to the family of Patient 25, but was refused because the boy is asymptomatic.

Late Mortality

There were six late postoperative deaths (Fig. 8): two 2 and 7 years, respectively, after operation, from progressive pulmonary vascular obstructive disease; two 6 months and 2 years, respectively after operation in patients who had complete heart block intraoperatively and had had a pacemaker implanted; one, 3 months after operation from Candida endocarditis; and one sudden and unexplained, 2 years after operation. Five of the six late deaths occurred in the first 15 patients in our series. In the later group, no patient had surgical complete heart block, and surgery was performed before the development of irreversible pulmonary vascular changes.

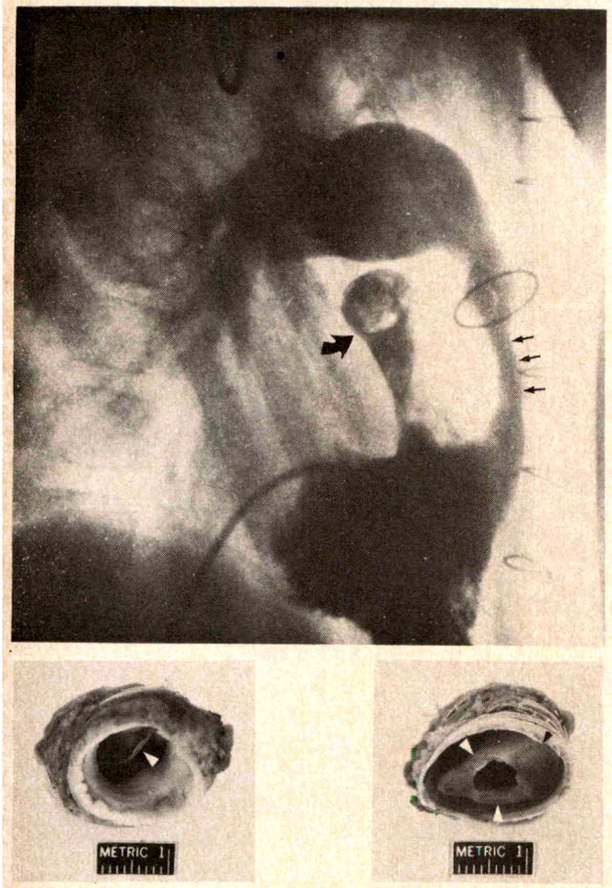

FIGURE 5. Patient 20. **Top,** lateral view of right ventriculogram 3.4 years after operation; note native pulmonary artery and pulmonary valve (**large arrows**). Because of a large gradient across a region of the valved conduit (**small arrows**), the conduit was replaced. **Bottom left,** view into the replaced conduit, distal to the porcine heterograft valve. The leaflets (**arrowhead**) are thin. **Bottom right,** view into the conduit proximal to the heterograft valve; note the fibrocalcific reaction (**arrowheads**), which shrank away from the conduit during fixation. The diameter of the effective orifice is about one third of that of the conduit.

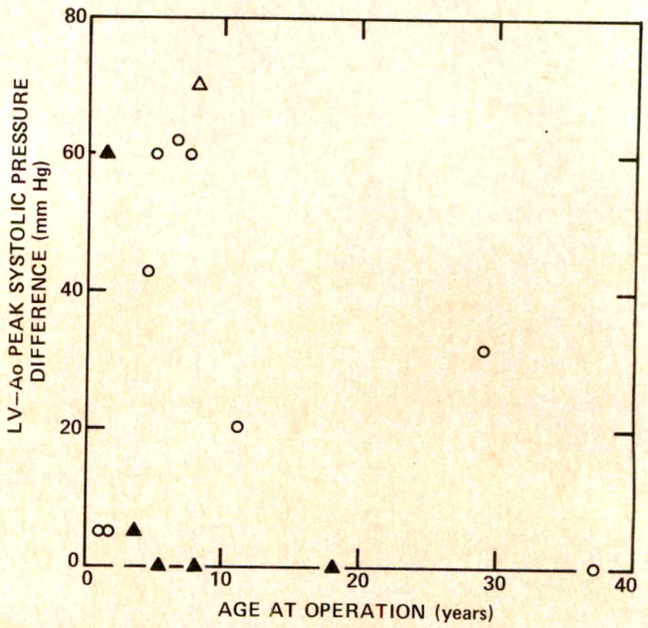

FIGURE 6. Peak systolic pressure gradient between the body of the left ventricle (LV) and the aorta (Ao), measured at postoperative cardiac catheterization, plotted against age at operation. Symbols as in Figure 1.

Discussion

Factors related to surgical mortality: Earlier reports[2–5,9,10] emphasized several factors related to surgical mortality, including size and complexity of the lesion, pulmonary vascular resistance, previous palliative procedures and experience with the surgical procedure. In our series, the major factor related to early mortality was small patient size: The risk of surgical death was 7 times higher in patients who weighed less than 10 kg than in patients who weighed more than 10 kg. Mortality was also greater in patients with the most complex combination of lesions: Only one of the five patients with double outlet right ventricle and subpulmonary ventricular septal defect is still alive. Neither pulmonary vascular resistance nor previous palliative procedures affected early surgical mortality. However, the two patients with the highest pulmonary vascular resistance, both of whom had had a prior systemic to pulmonary arterial shunt procedure, subsequently died.

Experience with the surgical procedures influenced outcome in two conflicting ways. There was a reduction in late mortality in our last 15 patients compared with that in our first 15: The electrophysiologic abnormalities in the early group did not occur in the later group, and the latter patients were operated on before irreversible pulmonary vascular resistance change developed. Conversely, because of the current emphasis on early repair of intracardiac defects, the later group of patients contained a larger proportion of children who weighed less than 10 kg, a group that continues to have an excessive early mortality.

Postoperative morbidity: Although mortality is a necessary consideration in assessing the risks of surgery, postoperative morbidity is also important. All of our 17 current survivors are asymptomatic, and many have achieved a significant augmentation in weight gain. Previous reports[4–6,11,12] of the intraventricular baffle procedure have described electrophysiologic and hemodynamic abnormalities, and both have occurred in our patients. Hemodynamic abnormalities include obstruction to outflow from both ventricles, residual intracardiac shunts and pulmonary hypertension. Significant electrophysiologic abnormalities were present in only five of our patients, although two with surgically induced complete heart block died, and a third requires digoxin to control supraventricular tachyarrhythmias.

Only two patients had virtually no hemodynamic abnormalities. Only five have had hemodynamic find-

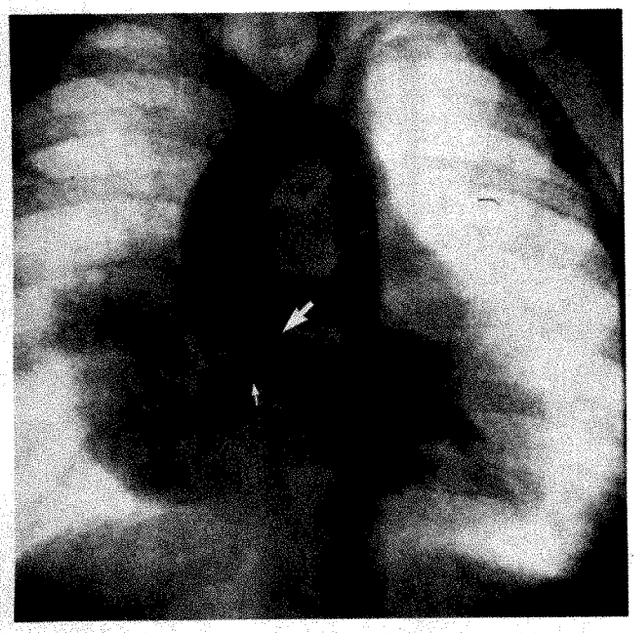

FIGURE 7. Patient 17. Frontal view of postoperative left ventriculogram. Obstruction to outflow (**large arrow**) is seen in the intraventricular baffle below the aortic valve. In addition, there is a trivial shunt (**small arrow**) from the left ventricle to right atrium.

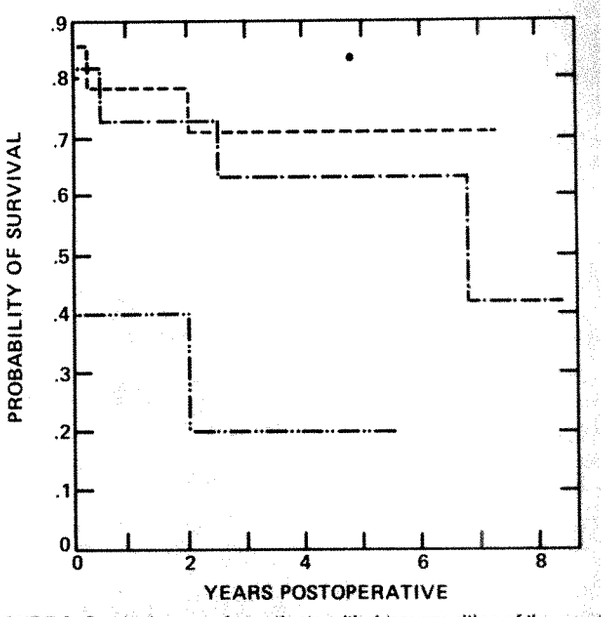

FIGURE 8. Survival curves for patients with d-transposition of the great arteries and ventricular septal defect (– –), double outlet right ventricle and subaortic ventricular septal defect (–·–) and double outlet right ventricle and subpulmonary ventricular septal defect (—··—).

ings severe enough to warrant reoperation, although we anticipate that more patients will be reoperated on as they grow. There has been no additional mortality in the four patients who were reoperated on to date.

Recommended guidelines for surgical treatment: On the basis of this series, we have adopted the following approach to treatment of patients with d-transposition of the great arteries and ventricular septal defect or double outlet right ventricle and ventricular septal defect. Because of the high mortality rate of intracardiac surgery in patients who weigh less than 10 kg, a palliative procedure is performed in infants refractory to medical management. Palliative procedures include (1) a systemic to pulmonary arterial shunt, preferably from the subclavian to the pulmonary artery,[16] for inadequate pulmonary blood flow, and (2) a pulmonary arterial band[17] for patients with excessive pulmonary blood flow. In patients weighing more than 10 kg, intracardiac surgery may be deferred if the pulmonary pressure is not elevated. We agree with others[2,9] that mid childhood is the optimal time for surgical repair with intraventricular baffle. Patients with double outlet right ventricle and subpulmonary ventricular septal defect present an especially difficult problem and we recommend an intraatrial baffle and closure of the ventricular septal defect,[18] rather than an intraventricular baffle alone to achieve a physiologic repair. The intraatrial baffle procedure has also been used in patients with d-transposition of the great arteries and ventricular septal defect,[19] but the mortality has been higher than that in our patients, and our patients have the additional advantage that the left ventricle provides systemic output. After the intraventricular baffle procedure electrophysiologic irregularities are occasionally seen, although not as frequently as after the intraatrial baffle procedure.[20] Because noninvasive evaluation does not predict the degree of residual disease, we suggest cardiac catheterization for all patients and advise reoperation when it is hemodynamically indicated.

In spite of the problems associated with the intraventricular baffle procedure, we believe that the overall improvement outweighs the risks of the procedure. Symptoms have been alleviated and hemodynamic status improved in all of our patients, and the younger patients have achieved a significant augmentation of growth.

Addendum

Since this report was submitted, Patients 3 and underwent recatheterization 5.8 and 5.9 years, respectively, after operation. In both patients, right ventricular pressures were at systemic levels or higher, as a result of obstruction in the external conduits. Both successfully underwent conduit replacement, but Patient 3 had a sudden unexplained death 4 months after reoperation.

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Idiopathic Recurrent Sustained Ventricular Tachycardia in Children and Adolescents

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The electrophysiologic characteristics of recurrent sustained ventricular tachycardia were studied in seven pediatric patients. The mechanisms of the ventricular tachycardia were evaluated using programmed electrical stimulation. Ventricular tachycardia could be reproducibly initiated in two patients and terminated in one patient in the basal state. It could be initiated in one additional patient and terminated in two additional patients after administration of a type IB drug. In four patients, ventricular tachycardia could not be initiated or terminated by programmed electrical stimulation. The site of origin of the ventricular tachycardia determined by catheter endocardial mapping was the right ventricular outflow tract in four patients, the interventricular septum in two patients and the inferior left ventricle in one patient. The ventricular tachycardia more frequently had an automatic than a reentrant mechanism, and originated more often in the right than in the left ventricle; it was not frequently associated with structural heart disease in this group of patients.

Ventricular tachycardia is an uncommon arrhythmia in children and adolescents and little information is available regarding its electrophysiologic characteristics or mechanisms. In adult patients, the mechanisms of recurrent sustained ventricular tachycardia have recently been studied with programmed electrical stimulation and activation mapping.[1–7] This study describes the electrophysiologic characteristics of recurrent sustained ventricular tachycardia in a group of pediatric patients.

Methods

Study Patients

Seven patients with recurrent sustained ventricular tachycardia were evaluated utilizing programmed electrical stimulation and catheter endocardial mapping (Table I). Of this group, six were male and one female. The age at documentation of the arrhythmia ranged from 5 to 18 years (mean ± standard deviation 12.3 ± 6) and the age at electrophysiologic study ranged from 7 to 21 years (mean 14.9 ± 6).

The diagnosis of ventricular tachycardia was made using standard electrocardiographic criteria[8] and confirmed in all cases by intracardiac recording during the arrhythmia demonstrating (1) the absence of His bundle deflection consistently preceding ventricular depolarization (seven patients), and (2) atrial capture normalizing the QRS configuration (five patients).

All seven patients had recurrent spontaneous episodes of ventricular tachycardia that were sustained for minutes to days with each patient having at least four spontaneous episodes of tachycardia before the electrophysiologic study. Only patients who fulfilled these criteria were included in this study. The patients with only short (less than five ventricular premature depolarizations) nonsustained runs of ventricular tachycardia were not included. In the 4 year interval during which the patients were studied, only three pediatric patients with congenital heart disease and recurrent sustained ventricular tachycardia were seen and studied. Findings in two of these patients who had correction of tetralogy of Fallot are reported elsewhere. The third patient had idiopathic hypertrophic subaortic stenosis.

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TABLE 1

Clinical Data in Seven Cases

Case	Sex	Age of Patient (yr)		Cardiac Diagnosis	ECG	Spontaneous Ventricular Tachycardia		
		At Onset	At Study			Configuration	Axis (°)	CL (ms)
1	M	7	7	None	WNL	LBBB	+75	330
2	F	7	8	None	WNL	LBBB	+90	480
3	M	5	10	None	WNL	LBBB	−60	440
4	M	16	18	None	WNL	RBBB	−100	360
5	M	18	22	None	IRBBB, LAH, 1° AVB	LBBB	+90	400
6	M	17	22	CAA	SB, IACD, IRBBB	RBBB	−60	460
7	M	16	17	None	WNL	RBBB	−30	400

AVB = atrioventricular block; CAA = coronary artery anomaly; CL = cycle length; ECG = electrocardiographic findings; IACD = intraatrial conduction delay; IHSS = idiopathic hypertrophic subaortic stenosis; IRBBB = incomplete right bundle branch block; LAH = left anterior hemiblock; LBBB = left bundle branch block; RBBB = right bundle branch block; SB = sinus bradycardia; WNL = within normal limits.

The resting electrocardiogram was normal in five patients and revealed incomplete right bundle branch block in two patients, with first degree atrioventricular (A-V) block in one. No patient had a prolonged Q-T interval or preexcitation.

Hemodynamic and angiographic catheterization studies were performed in all patients. Six patients had completely normal studies and one patient had anomalous origin of the right coronary artery from the left aortic cusp with no hemodynamic abnormality.

Electrophysiologic Studies

Studies were performed in the postabsorptive state after written informed consent had been obtained. Three patients were sedated with Nembutal® (4 mg/kg) and morphine sulfate (0.15 mg/kg). The remaining patients received no sedation. Three to six electrode catheters were inserted percutaneously or by cutdown and positioned using biplane fluoroscopy. The number of recording sites varied but usually included the high right atrium; the left atrium or coronary sinus; the A-V junction at the His bundle site; the right ventricle at the apex, septum, inflow, free wall and outflow tract; and the left ventricle at the apex, septum, lateral wall and base. Standard quadripolar electrode catheters with 1 cm interelectrode distance (USCI, Billerica, Massachusetts) were used to record and stimulate from a specific site. A tripolar catheter was used to obtain the His bundle electrogram.

Stimulation was performed using a specially designed programmable stimulator and an optically isolated constant current source. The stimuli were rectangular pulses 1 ms in duration at twice diastolic threshhold (0.75 to 2 mA). Intracardiac recordings from several sites were simultaneously recorded with three surface electrocardiographic leads and time lines. Intracardiac electrograms were filtered at 40 to 500 hertz. The data were stored on magnetic tape and later retrieved on photographic paper at speeds of 150 to 400 mm/s.

Protocol for programmed stimulation: Ventricular tachycardia, either induced or spontaneous, was present during the electrophysiologic study in all patients.

The following protocol of programmed stimulation was used in each patient:

1. Atrial pacing at incremental rates (cycle length 600 to 250 ms).
2. Premature atrial stimuli during sinus rhythm or atrial pacing, or both.
3. Ventricular pacing at incremental rates (cycle length 750 to 250 ms).
4. Premature ventricular stimuli during sinus rhythm or ventricular pacing, or both. If one premature ventricular stimulus (S_2) scanning from late diastole to ventricular refractoriness did not initiate ventricular tachycardia, scanning with a second premature stimulus (S_3) was then employed. Double premature stimuli (S_2, S_3) were introduced starting at an S_1-S_2 interval 50 to 100 ms longer than the ventricular effective refractory period with the S_2-S_3 interval equal to the S_1-S_2 interval. The S_2-S_3 interval was shortened, and when S_3 failed to evoke a V_3, the S_1-S_2 interval was decreased until S_3 could evoke a response or ventricular tachycardia. This method was used until both S_2 and S_3 reached refractoriness. Stimulation was performed at the right ventricular apex in all patients. In addition, stimulation was performed in the right ventricular outflow tract (six cases) and the left ventricle (seven cases).
5. During ventricular tachycardia, programmed single or double ventricular extrastimuli and rapid ventricular pacing were used in an attempt to terminate the arrhythmia. The extrastimuli were introduced from several different sites including the left ventricle.

Endocardial mapping: Endocardial catheter mapping was performed using one or more 6 French ventricular catheters as exploring electrodes. The mapping sites included fixed sites usually consisting of the A-V junction, the left atrium or the coronary sinus and the high right atrium. The catheter in the right ventricular apex was left in a stable position whenever possible as a reference electrode. The additional mapping sites included the mid septum, anterior wall, outflow tract, lateral inflow tract of the right ventricle and the septum, apex, anterior and lateral walls and inferobasal area of the left ventricle. Two reference points were utilized: one, the earliest onset of the QRS complex in any of the recorded electrocardiographic leads, and the other, a ventricular electrogram recorded from a fixed ventricular site (A-V junction or right ventricular apex). The interval measurement was taken at the point at which the most rapid deflection crossed the baseline,[9,10] using the mean value of six consecutive beats. The earliest site of activation during tachycardia was considered the site of origin of the tachycardia.

Response to antiarrhythmic drugs: This was determined in all patients. The study included the intravenous administration of one or more of the following drugs: (1) lidocaine, 1

TABLE II

Electrophysiologic Data in Seven Cases

Case	A-H	H-V	$ERP_{600}RV$	$ERP_{600}LV$	Induced Ventricular Tachycardia	
					Configuration	CL (ms)
1	125	30	250	260	LBBB	350
2	65	40	180	180	...	...
3	50	90	220	235	...	...
4	85	42	240	240	RBBB	350
5	78	45	190	185	...	...
6	...	...	235	240	RBBB	460
7	...	...	...	...	...	...

CL = cycle length; $ERP_{600}LV$ = effective refractory period of the left ventricle at a cycle length of 600 ms; $ERP_{600}RV$ = effective refractory period of the right ventricle at a cycle length of 600 ms; LBBB = left bundle branch block; RBBB = right bundle branch block.

to 2 mg/kg at 25 mg/min; (2) phenytoin, 5 to 10 mg/kg at 20 mg/min; and (3) procainamide, 10 to 15 mg/kg at 50 mg/min. Levels of phenytoin or procainamide were obtained at the time of demonstrated electrophysiologic effect. Programmed stimulation was repeated immediately on completion of the drug infusion.

Criteria for reentrant versus automatic tachycardia: The criteria used in the present study to define reentrant tachycardia have been discussed by Wellens et al[2,3] and include (1) initiation of tachycardia during cardiac pacing by one or two premature beats within a well defined and reproducible zone of coupling intervals (echo zone); (2) termination of tachycardia by one or two premature stimuli within a well defined and reproducible zone of coupling intervals; and (3) prolongation of the interval from stimulus to first complex of the tachycardia with increasing prematurity of the initiating stimulus.

The criteria used to define automatic tachycardia have been described by Goldreyer et al.[11] *and include:* (1) initiation of tachycardia in the absence of any relation to timing of the premature stimulus; (2) initiation of tachycardia by an impulse falling late in diastole outside the relative refractory period of the ventricle; and (3) absence of reproducible termination of tachycardia by programmed electrical stimulation.

Results

Basal electrophysiologic data: A-H and H-V intervals could be obtained in five patients (Table II). In one patient with azygous continuation of the inferior vena cava, a His bundle deflection could not be obtained because of difficulty with catheter manipulation. In a second patient, A-H and H-V intervals could not be obtained because of incessant ventricular tachycardia throughout the study. The A-H intervals were normal in the five patients. The H-V intervals were normal for age in four patients and prolonged in one patient who had intermittent infra-His block (Case 3).

Sinus nodal function was normal as determined by sinus nodal recovery time[12] and sinoatrial conduction time in six patients. One patient had severe sinus nodal dysfunction. Atrial function as determined by the atrial refractory period[13] was normal in all patients.

A-V nodal function was normal in six patients. Wenckebach cycle lengths were less than 400 ms in each of these patients. One patient exhibited infra-His block at a cycle length of 350 ms.

Electrocardiographic characteristics of ventricular tachycardia: The cycle length of the spontaneous ventricular tachycardia was 330 to 480 ms (mean 410 ± 54). In five of the patients who had spontaneous ventricular tachycardia during the study, the first ventricular tachycardia complex, which was similar in configuration to the subsequent tachycardia complexes, followed the last sinus complex with a relatively long R-R interval (greater than 75 percent of the R-R interval). Two patients had fusion complexes and all patients had A-V dissociation during ventricular tachycardia.

Initiation of ventricular tachycardia: Ventricular tachycardia could be initiated reproducibly in two patients in the basal state (Table III), by rapid ventricular pacing in one (Case 6) and by single ventricular stimuli and rapid ventricular pacing in the other patient (Case 4). In an additional patient (Case 1), the tachycardia could not be initiated in the basal state but could be initiated by single ventricular premature stimuli after administration of lidocaine (Fig. 1).

Ventricular tachycardia could not be initiated in the remaining four patients by any method utilized including rapid atrial and ventricular pacing, and single

TABLE III

Initiation and Termination of Ventricular Tachycardia in Seven Cases

Case	Mode of Initiation			Mode of Termination		
	1VPD	2VPD	VP	1VPD	2VPD	VP
1	+	...	...	+	...	+
2	−	−	−	−	−	−
3	−	−	−	−	−	−
4	+	...	+	+	...	+
5	−	−	−	−	−	−
6	−	−	+	+	...	+
7	−	−	−	−	−	−

+ = successful; − = unsuccessful; VP = ventricular pacing; VPD = ventricular premature depolarization.

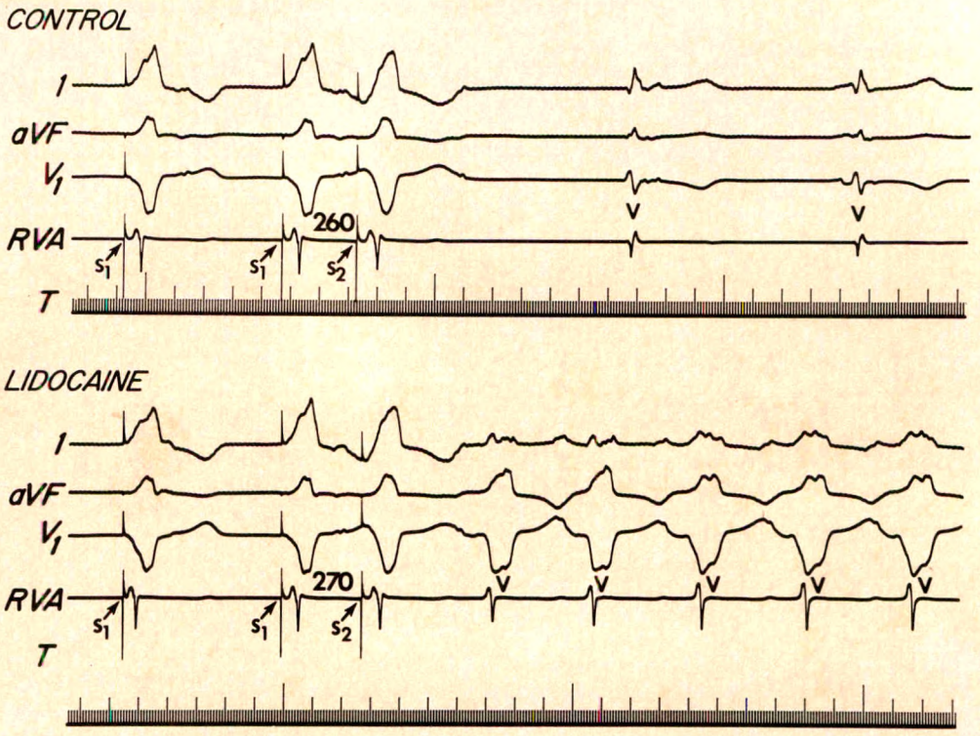

FIGURE 1. Patient 1. Initiation of ventricular tachycardia only after lidocaine infusion. In both panels, electrocardiographic leads I, aVF and V_1 are shown with a right ventricular apical (RVA) electrogram and 10 ms time (T) lines. Stimuli are indicated by **arrows.** In the **upper panel** during control conditions, a single premature stimulus (S_2) delivered during ventricular pacing at a cycle length of 550 ms (S_1-S_1) failed to initiate ventricular tachycardia. No other stimulation protocol initiated ventricular tachycardia during control conditions. After an infusion of lidocaine (30 mg) **(lower panel),** a single premature stimulus initiated ventricular tachycardia reproducibly. After elimination of lidocaine, ventricular tachycardia was no longer inducible by programmed stimulation.

and double ventricular premature stimulation both in sinus rhythm and during ventricular pacing from multiple sites including the right ventricular outflow tract, right ventricular apex and left ventricular apex.

Response to programmed stimulation during ventricular tachycardia: Ventricular tachycardia could be terminated reproducibly in one patient (Case 6) by single ventricular premature stimuli or rapid ventricular pacing. In one patient (Case 1), the tachycardia could not be terminated in the basal state but could be terminated by single ventricular premature depolarizations after administration of lidocaine (Fig. 2). In one additional patient (Case 4), the tachycardia could be terminated intermittently in the basal state but at other times required the administration of phenytoin for reproducible termination.

In the remaining four patients, ventricular tachycardia could not be terminated by electrical stimulation either before or after drug administration. In these four patients, ventricular stimulation did not terminate tachycardia but reset it, resulting in a pause followed by a gradual warm-up of tachycardia (Fig. 3).

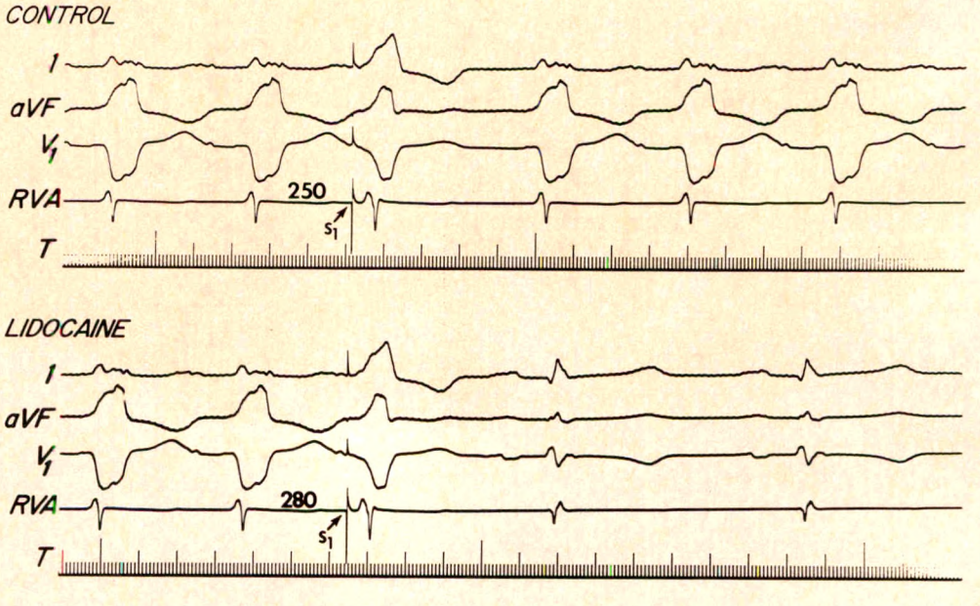

FIGURE 2. Patient 1. Termination of ventricular tachycardia by programmed stimulation after administration of lidocaine. The format in each panel is the same as in Figure 1. In the **upper panel,** a single programmed extrastimulus (S_1) delivered at a coupling interval of 250 ms failed to terminate ventricular tachycardia. This was the shortest interval at which a single extrastimulus captured the ventricles. No other stimulation technique was capable of terminating ventricular tachycardia. After lidocaine infusion **(lower panel)** a single extrastimulus (S_1) at a coupling interval of 280 ms terminated ventricular tachycardia. After metabolism of lidocaine, programmed stimulation failed to terminate ventricular tachycardia.

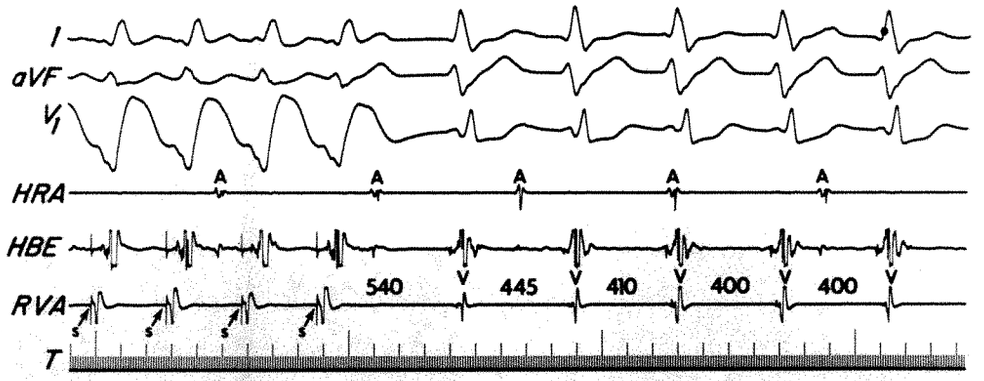

FIGURE 3. Patient 7. Demonstration of "warm-up" of ventricular tachycardia after overdrive pacing. Electrocardiographic leads I, aVF and V_1 are displayed with bipolar electrograms recorded in the high right atrium (HRA), His bundle area (HBE) and right ventricular apex (RVA) and 10 ms time (T) lines. Pacing stimuli (s) are indicated by **arrows** and the interelectrogram intervals are indicated in milliseconds. Right ventricular pacing at a cycle length of 300 ms was begun during ventricular tachycardia (not shown) and discontinued after 30 seconds at the fourth stimulus. Ventricular tachycardia persisted. Note that the tachycardia cycle length progressively discussed over four cycles until it returned to the control cycle length of 400 ms present before pacing.

Atrial pacing in five patients resulted in ventricular capture converting the QRS complex to a supraventricular configuration without termination of ventricular tachycardia. Another patient had spontaneous sinus captures without termination of arrhythmia. Ventricular pacing could capture the ventricles in all patients without interrupting ventricular tachycardia.

Endocardial mapping and sites of origin: The QRS configuration of the ventricular tachycardia was right bundle branch block in three patients and left bundle branch block in four (Fig. 4). The site of origin of ventricular tachycardia was the right ventricular outflow tract in the four patients with left bundle branch block configuration (Table IV). The configuration of these ventricular tachycardias originating in the right ventricular outflow tract was similar in these four patients. The site of origin in the three patients with right bundle branch block configuration was the inferobasal wall of the left ventricle, the mid right ventricular septum and the mid left ventricular septum respectively (Fig. 5). Confirmation of mapping data was obtained by pacing from the site of origin, which produced a QRS configuration similar to that of the spontaneous ventricular tachycardia.

Discussion

Ventricular tachycardia is an uncommon arrhythmia in childhood, although our recent experience suggests that it is more common than is generally appreciated

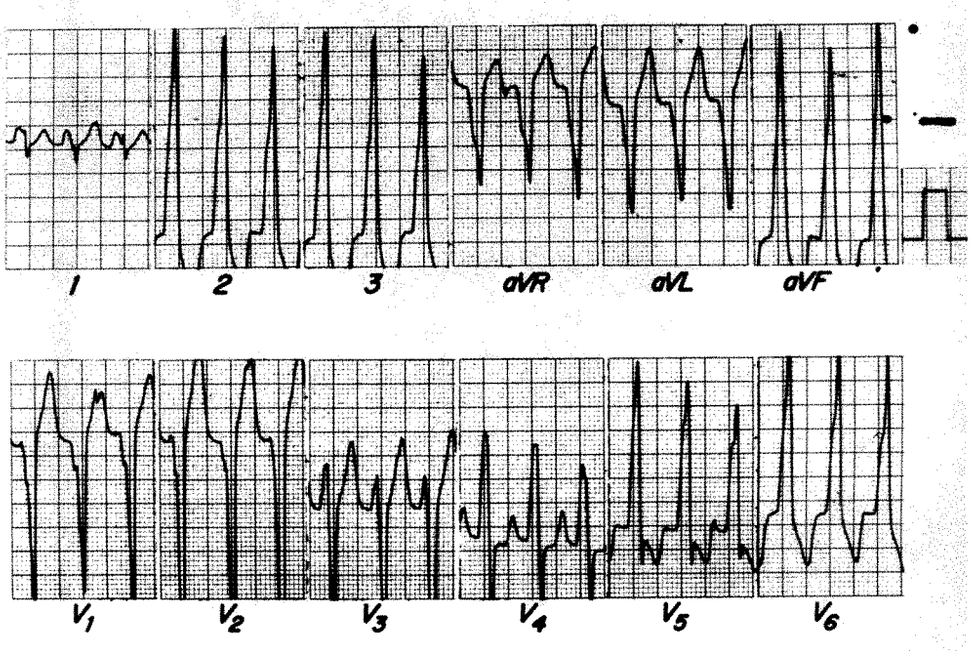

FIGURE 4. Patient 5. Electrogram during ventricular tachycardia. It is typical of the ventricular tachycardias with a left bundle branch block configuration observed in this group of patients. The right precordial leads show an rS or QS pattern, and the limb leads show an inferior axis with all monophasic R waves in leads II, III and aVF.

TABLE IV

Site of Origin of Ventricular Tachycardia in Seven Cases

Case	Configuration Mapped	Site of Origin
1	LBBB	RVOT
2	LBBB	RVOT
3	LBBB	RVOT
4	RBBB	RIVS
5	LBBB	RVOT
6	RBBB	LV, inferobasal
7	RBBB	LIVS

LBBB = left bundle branch block; LIVS = left endocardial surface of the interventricular septum; LV = left ventricle; RBBB = right bundle branch block; RIVS = right endocardial surface of the interventricular septum; RVOT = right ventricular outflow tract.

Although various reports of ventricular tachycardia in children have attributed the arrhythmia to congenital or acquired heart disease,[14,15] myocarditis,[16] metabolic disturbances,[17] cardiac catheterization or surgery[18] or drug toxicity, other reports have found no known etiology or structural heart disease.[19,20] The findings in our series of seven patients are consistent with the studies in which structural heart disease is uncommon. One of our patients had a coronary arterial abnormality of undetermined significance, whereas six of the seven patients had completely normal angiographic and hemodynamic studies.

Ventricular tachycardia in children versus adults: Limited electrophysiologic data are available concerning ventricular arrhythmias in children.[21–23] No activation studies or mapping data during ventricular tachycardia have been reported. Early reports of ventricular tachycardia in children provided clinical information including abbreviated electrocardiographic recordings. Many of the electrocardiograms during ventricular tachycardia in the earlier reports bear a striking resemblance to each other. The most common QRS configuration has been left bundle branch block pattern of tachycardia, usually occurring in children with a normal heart. The right bundle branch configuration was reported primarily in children with left ventricular structural abnormalities, most notably cardiac tumors.[24] In contrast to findings in the pediatric age group, ventricular tachycardia in adults usually occurs in association with structural heart disease. Coronary artery disease with or without a ventricular aneurysm is the most common abnormality.[6,25,26] Arrhythmogenic right ventricular dysplasia with ventricular tachycardia has also been described in adults.[27] There are a few reports of adults with no heart disease with "idiopathic" ventricular tachycardia, but these reports represent less than 10 percent of adult patients with ventricular tachycardia.[20,28–30] The presence of structural heart disease and the right bundle branch pattern of ventricular tachycardia in adults strongly contrasts with the absence of structural heart disease and the left bundle branch block pattern of ventricular tachycardia in children.

Endocardial catheter mapping of the ventricles in adults has been reported.[7] The most common site of origin of ventricular tachycardia was the left ventricle, particularly in an aneurysm of the left ventricle when this was present. In contrast, the most common site of origin of ventricular tachycardia in our children was the right ventricle, especially the right ventricular outflow tract.

Reentrant tachycardia in children versus adults: The mechanisms of ventricular tachycardia in adults have been studied by several investigators.[1–7] Wellens et al.[2,3] suggested that initiation and termination of the arrhythmia by stimulation and an inverse relation of the initiating coupling interval and the interval of the first complex of the tachycardia indicate a reentrant mechanism. On the basis of these criteria, 70 to 95 percent of adult patients with ventricular tachycardia have reen-

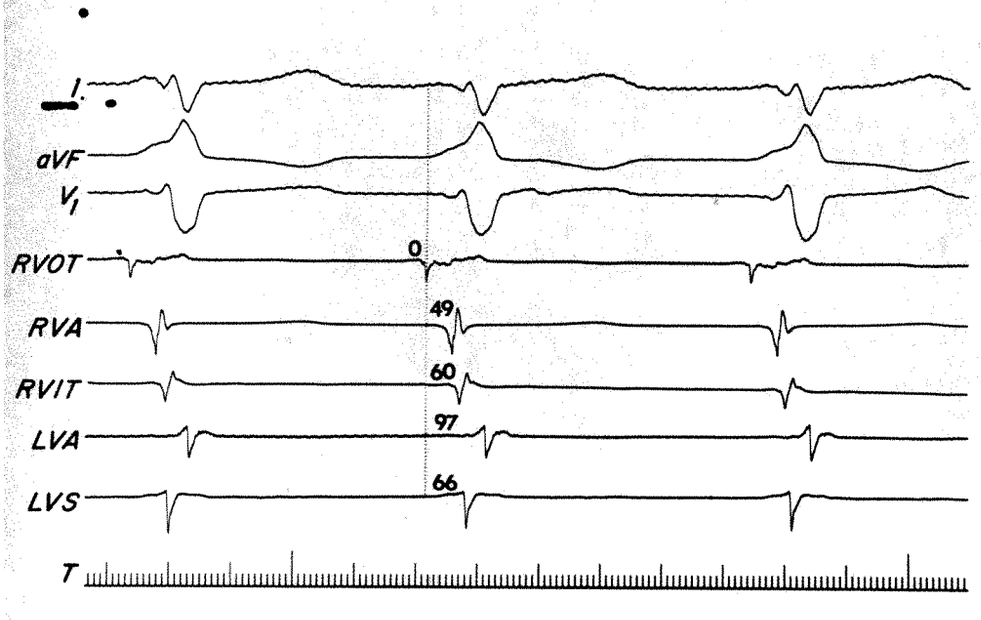

FIGURE 5. Patient 2. Ventricular endocardial mapping during ventricular tachycardia. Electrocardiographic leads I, aVF and V_1 are shown with bipolar electrograms recorded at the right ventricular outflow tract (RVOT), the right ventricular apex (RVA), the right ventricular inflow tract (RVIT), the left ventricular apex (LVA) and the left ventricular septum (LVS) and 10 ms time (T) lines. The **dotted line** indicates the onset of the QRS complex and the numbers indicate activation times (ms) measured from the onset of the QRS complex. Ventricular tachycardia was present and the earliest electrical activity was recorded in the right ventricular outflow tract. The earliest left ventricular electrograms were recorded on the left side of the intraventricular septum. No other site in this patient was activated earlier than the right ventricular outflow tract.

trant ventricular tachycardia.[31] A few investigators[4,32] have not been able to confirm these results, particularly in patients with a very recent myocardial infarction. Others[33] have suggested that programmed electrical stimulation may also induce an unusual type of automatic tachycardia caused by triggered automaticity. This type of automaticity, in contrast to the usual type of enhanced phase 4 automaticity, requires an initiating stimulus that triggers a self-sustaining automatic discharge. To date, no evidence of triggered automaticity has been shown in human ventricular tissue.

Ventricular tachycardia in our patients was infrequently initiated and terminated by programmed electrical stimulation. Tachycardia fulfilled the criteria for reentry in only two patients. In one additional patient, the criteria for reentry were fulfilled only after administration of drugs. The significance of initiation and termination only after administration of drugs is unclear. The tachycardias in the other four children, in contrast, did not meet the criteria for a reentrant mechanism and had characteristics of automatic ventricular tachycardia as described by Goldreyer et al.[11] Thus, less than half of the children (three of seven) had studies suggesting a reentrant mechanism, whereas approximately 90 percent of adult patients fulfill the criteria for reentrant ventricular tachycardia.

Clinical implications: The differences in the frequency of the reentrant mechanism of ventricular tachycardia in children and adults and the differences in the anatomic substrates necessitate differences in evaluation and therapy. The presence of automatic ventricular tachycardia or lack of a reproducible initiation of tachycardia makes the laboratory evaluation of pharmacologic therapy utilizing electrophysiologic study, as was recently described in adults, much less useful in most children than in adults.[32,34–37] This method of evaluation is only useful in the presence of a reentrant ventricular tachycardia that can be reproducibly initiated and terminated.

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Clinical Course of Cardiovascular Involvement in the Mucocutaneous Lymph Node Syndrome

Relation Between Clinical Signs of Carditis and Development of Coronary Arterial Aneurysm

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Seventy-nine patients with mucocutaneous lymph node syndrome were evaluated prospectively by clinical examination, electrocardiography, chest radiography, M mode and two dimensional echocardiography and thallium-201 myocardial scanning. Serial changes were categorized according to the duration of illness: stage I (1 to 10 days), stage II (11 to 20 days), stage III (21 to 30 days), stage IV (31 to 60 days) and stage V (61 days to 40 months). The presence of myocarditis in stages I and II was suggested in 40 of 79 patients (50.6 percent) by electrocardiographic, echocardiographic, radiographic and clinical abnormalities. Myocarditis was accompanied by pericarditis in six patients and by both endocarditis and pericarditis in one patient. These signs of inflammation were resolved by stage III in all but three patients with electrocardiographic abnormalities. In the active stage, large coronary arterial lesions were suspected only because of an abnormal spherical echo-free space in the region of the coronary arteries on two dimensional echocardiograph as well as electrocardiographic evidence of deep Q waves in leads II, III and aVF. One or more coronary aneurysms developed in 11 patients, primarily in stage II; regression of the aneurysm was noted in 5 of these patients during stages III, IV and V. Aneurysm regression demonstrated by angiography did not correlate with echocardiographic changes in aneurysm size in one patient. Moreover, the occurrence of coronary aneurysm did not correlate with the presence of signs of carditis, because the frequency of carditis was the same in patients with and without aneurysm.

The mucocutaneous lymph node syndrome (Kawasaki's disease) is a clinical entity consisting of high fever, mucocutaneous involvement and cervical lymphadenopathy that affects infants and young children.[1] The acute inflammatory features consist of angiitis with involvement of multiple organ systems.[2] It has been suggested[2–7] that the pathologic changes are indistinguishable from those observed in infantile periarteritis nodosa.[2–4] Although this syndrome is predominantly found in Japan, it has become increasingly recognized in other countries.[5–10] Carditis and coronary arterial lesions have frequently been demonstrated in association with mucocutaneous lymph node syndrome.[11–13] However, the natural history of carditis and coronary arterial aneurysms is unclear. Furthermore, to our knowledge, there are no clinical data that evaluate serially the relation between carditis and coronary aneurysms. Thus the present study was undertaken to determine the natural history of the cardiovascular aspects of mucocutaneous lymph node syndrome and particularly, to evaluate the relation between signs of carditis and the development of coronary arterial abnormalities.

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Methods

Clinical criteria and diagnosis: Seventy-nine patients admitted to Kitasato University Hospital between November 1976 and November 1979 were evaluated prospectively. There were 53 male and 26 female patients aged 3 months to 10 years (mean 2.7 years). The diagnosis of mucocutaneous lymph node syndrome was made on the basis of criteria proposed in 1972 by the Japanese Mucocutaneous Lymph Node Syndrome Research Committee.[14]

The clinical course was categorized according to the duration of illness as follows: stage I (1 to 10 days), stage II (11 to 20 days), stage III (21 to 30 days), stage IV (31 to 60 days) and stage V (61 days to 40 months). The onset of illness was defined as the day of the first diagnostic symptom. The duration of fever, heart sounds, heart murmur, friction rub and erythrocyte sedimentation rate were evaluated serially. Electrocardiography, chest radiography and M mode and two dimensional echocardiography were performed in all patients on admission (stage I) and at least once a week during stages I through III of the disease and occasionally through stage IV. Thallium-201 myocardial scanning was performed in 48 patients one to three times during the course of their illness. The diagnosis of carditis was entertained when clinical signs such as gallop rhythm, heart murmur, friction rub and laboratory signs of an abnormal electrocardiogram, radiogram and echocardiogram were observed.[15] The major criterion for angiography was two dimensional echocardiographic detection of coronary aneurysms. Other criteria included an abnormally high score on the table devised by Asai et al.[11] By these criteria, angiography was indicated in only 15 patients between 35 days and 5 months (mean 1.8 months) after the onset of the disease. Four patients underwent follow-up coronary angiography 1 to 3 years after the initial evaluation.

The following therapeutic programs were employed: (1) Antibiotic agents (aminobenzyl penicillin or cephaloridine, 100 mg/kg per day) were administered until bacterial infection was excluded. (2) Aspirin (30 to 50 mg/kg per day) was given until clinical evidence disappeared and the erythrocyte sedimentation rate returned to normal. (3) Glucocorticoid (prednisolone, 2 mg/kg per day), depending on the clinical gravity of the disease, was given until cardiac signs or prolonged fever disappeared. (4) Patients with coronary arterial lesions received aspirin (30 mg/kg per day) or warfarin (0.1 to 0.2 mg/kg per day) adjusted to 15 to 30 percent by Thrombotest (Quick prothrombin test), or both, during the existence of large coronary lesions.

Electrocardiography: Electrocardiograms were evaluated for changes compatible with myocarditis or pericarditis such as (1) P-R interval prolongation of 0.17 second or greater; (2) prolonged corrected Q-T interval (Q-Tc) of 0.425 second or greater; (3) R wave in V_6 of 0.6 mV or less; (4) R wave in lead V_1 of 0.4 mV or less; (5) amplitude of P wave of 0.25 mV or greater; (6) duration of P wave of 0.08 second or greater; (7) S-T segment depression of 0.1 mV or greater for 0.06 second or greater below the baseline; (8) S-T segment elevation of 0.2 mV or greater (except for right precordial leads); (9) T wave in lead V_6 of 0.1 mV or less (age less than 6 months), T wave in lead V_6 of 0.2 mV or less (age 6 months or greater); (10) evidence of myocardial ischemia or infarction, such as Q/R ratio of 0.3 or greater, increasing Q waves or ST-T changes or all three; (11) standard criteria for left or right ventricular hypertrophy; and (12) various arrhythmias.[15–17]

Chest radiography: The cardiothoracic ratio was measured serially on chest radiograms. Cardiomegaly was suggested by a cardiothoracic ratio greater than 55 percent or an increase of more than 5 percent in serial films, or both.[18]

M mode echocardiography: Echocardiograms were obtained with a commercially available ultrasonoscope (ALOKA SSD 200 or 100) (ALOKA Company Ltd., Tokyo) utilizing a 3.5 or 2.25 megahertz nonfocused transducer. The transducer was placed at the third or fourth intercostal space at the left parasternal border. The M mode scan from the aortic root to the apex of the left ventricle was recorded on Polaroid® film or by strip chart recorder. Left ventricular function was evaluated by calculation of percent fractional shortening, the ratio of posterior wall to septal excursion and B-B′ formation[19] on the anterior mitral leaflet. The echocardiogram was also assessed for pericardial effusion. The echocardiographic indexes of left ventricular performance were compared with normal values for children established in our laboratory, which are similar to those reported by others for normal children and adults.[20–22] Abnormal indexes were defined by a percent fractional shortening of 32 percent or less or a ratio of posterior wall to septal excursion of 3.5 or greater or less than 1.0. Pericardial effusion was diagnosed by visualizing separation of the epicardium from the pericardium in both systole and diastole.[23]

Two dimensional echocardiography: This procedure was performed using an electronic linear scanner with a 3.5 megahertz, 60 element transducer adjusted to focus at 4 and 7 cm (ALOKA SSD 200). Visualization of the main coronary arteries was accomplished in the manner reported previously by our group.[24] The diagnosis of coronary arterial aneurysm was made by visualization of a spherical or fusiform shape of the proximal portion of the main coronary arteries. Furthermore, a few days after initial study, patients with ultrasonic evidence of coronary aneurysm were reevaluated to establish the reproducibility of the echocardiographic findings.

Thallium-201 myocardial scanning: Myocardial images were obtained utilizing a high resolution scintillation camera (Pho Gamma HP and LFOV Gamma Camera) (Searle Company, Chicago) and a 140 keV parallel hole collimator or converging collimator, within 10 minutes of intravenous injection of 0.5 to 1 mCi of thallium-201 chloride. The images were recorded in the anteroposterior, left lateral and 30° left anterior oblique projections. Interpretation was undertaken without prior knowledge of clinical findings. A consistent decrease in myocardial uptake observed in at least two views was interpreted as abnormal.[25]

Left heart catheterization and angiography: After left ventricular pressures were recorded, left ventricular and aortic cineangiography were performed in the standard manner. Three patients underwent selective coronary angiography. Ejection fraction was calculated by the single plane area-length method.[26] Asynergy was assessed by the criteria of Herman and Gorlin.[27]

Results

Auscultatory signs: A gallop rhythm was audible transiently in stages I and II in 10 patients (12.6 percent). A significant heart murmur suggesting mitral regurgitation was found in only one patient in stage I and disappeared 5 days later. A friction rub was not observed.

Electrocardiography: Electrocardiographic abnormalities consisted of (1) prolongation of the P-R interval in 11 cases (13.9 percent); (2) prolongation of the Q-Tc interval in 18 cases (22.8 percent); (3) low amplitude R wave in lead V_1 or V_6 in 13 cases (16.5 percent); (4) low amplitude T wave in lead V_6 in 12 cases

(15.2 percent); and (5) ST-T wave changes in 8 cases (10.1 percent). Deep Q waves, P wave changes, left ventricular hypertrophy, right ventricular hypertrophy, sinus bradycardia, second degree atrioventricular (A-V) block and premature ventricular complexes each occurred in a small percent of cases. In serial electrocardiograms low amplitude R and T waves appeared in stages I and II and returned to normal by stage III. Abnormal S-T segment changes occurred primarily in stages I and II, and were resolved by stage IV. Transient arrhythmias such as sinus bradycardia (two patients) and second degree A-V block (one patient) were observed in stage II. In contrast, abnormal Q wave patterns (four patients) appeared in stages II and III and persisted to later stages. Of these four patients, one died suddenly in stage V. Premature ventricular complexes were also found in stage III in one patient with deep Q waves (Table I).

Chest radiography: A cardiothoracic ratio greater than 50 percent with an increase of greater than 5 percent in serial films was observed in 16 patients (20.3 percent). Cardiomegaly with a cardiothoracic ratio greater than 60 percent occurred in only two patients. These findings were seen in stages I and II with resolution by stage III (Table I).

M mode echocardiography: The abnormalities observed included (1) percent fractional shortening of 32 percent or less in 15 patients (19.0 percent), of whom 10 had shortening of less than 28 percent; (2) posterior wall to septal excursion ratio greater than 3.5 in 4 patients (5.1 percent); and (3) pericardial effusion in 7 patients (8.8 percent). No patient had either a posterior wall to septal excursion ratio of less than 1.0 or B-B′ formation. Each of the six patients with pericardial effusion had reduced percent fractional shortening. Abnormal echocardiographic indexes were observed in stages I and II and resolved by stage III (Table I).

Two dimensional echocardiography: Satisfactory visualization of the left main coronary artery was achieved in 75 patients (94.9 percent). The proximal portion of the right coronary artery was visualized well in only 14 patients (17.7 percent). Spherical or fusiform patterns, or both, in the main coronary arteries were observed in eight patients during stage II and in three during stage III. These patterns disappeared in two patients during stage III, in one patient during stage IV and in two patients during stage V. Echographic evidence of coronary arterial aneurysms persisted to stage V in seven patients. Among these seven patients, angiography imaged multiple aneurysms of the right and left coronary arteries in four, and a single aneurysm of the proximal portion of the left coronary arteries in three. Of the three patients in whom echographic evidence of left coronary arterial aneurysm disappeared by stage III or IV (Fig. 1), one had normal coronary arteries on aortography at the time of normal echographic examination. In four patients, initial and subsequent angiography confirmed the two dimensional echocardiographic evidence of coronary arterial aneurysms. The findings remained unchanged in two of the four pa-

TABLE I

Serial Changes of Abnormal Findings of Four Clinical Indexes (M mode echocardiogram, chest radiogram, gallop rhythm and heart murmur)

Indexes	Patients (n)	Appearance of Abnormal Findings (patients [n])		Disappearance of Abnormal Findings (patients [n])		
		I	II	III	IV	V
M mode echocardiography						
Reduced %FS	15	11/5	4/6	0/4	...	...
Increased PWe/LSe	4	3/1	1/2	0/1	...	...
Pericardial effusion	7	6/4	1/3	...	...	...
Electrocardiography						
Prolonged P-R interval	11	4/2	6/4	1/4	0/1	...
Prolonged Q-Tc interval	18	5/2	11/5	2/8	0/3	...
Low R wave	13	11/8	2/4	0/1	...	...
Low T wave	12	9/5	3/5	0/2	...	...
Abnormal S-T segment	8	4/2	3/3	1/2	0/1	...
High Q/R ratio with increased Q wave	4	...	2/0	2/0	0/1	0/2
Sinus bradycardia	2	...	2/1	0/1	...	...
2° atrioventricular block	1	...	1/0	0/1	...	...
PVC	1	...	...	1/0	0/1	...
Left ventricular hypertrophy	2	...	2/0	0/1	0/1	...
Right ventricular hypertrophy	1	...	1/0	0/1	...	...
Chest radiography						
Increased CTR	16	12/8	4/6	0/2	...	...
Presence of gallop rhythm	10	6/5	4/4	0/1	...	...
Mitral regurgitant murmur	1	1/1	...	...	...	...
Friction rub	0	0	...	...	...	...

CTR = cardiothoracic ratio; %FS = percent fractional shortening of the left ventricle; PVC = premature ventricular complex; PWe/LSe = ratio of left posterior wall to left septal excursion.

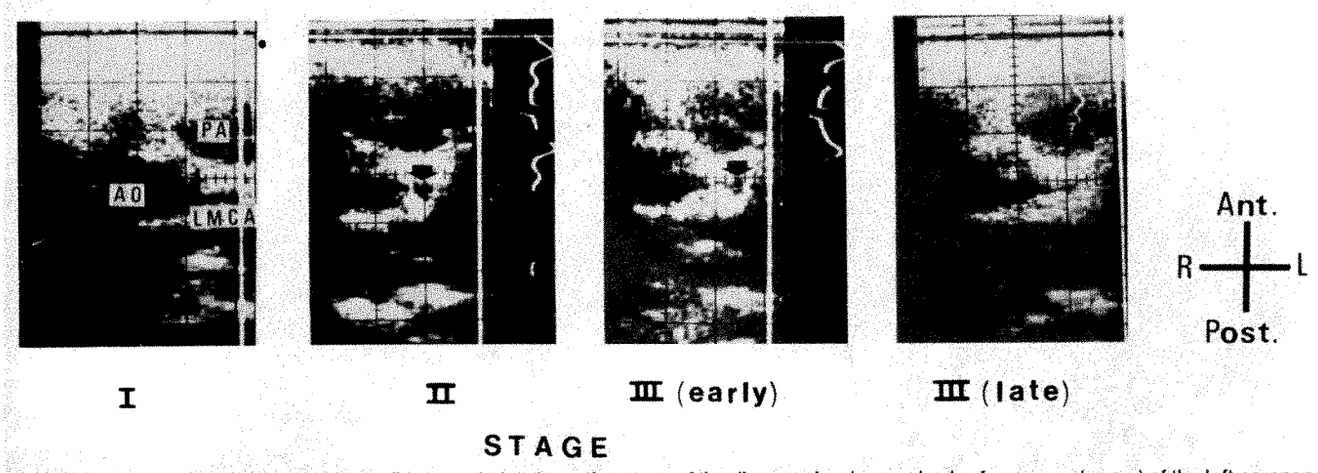

FIGURE 1. Serial two dimensional echocardiograms during the active stage of the disease. An abnormal echo-free space (**arrow**) of the left coronary artery was observed in stage II and disappeared during stage III. Ant. = anterior; AO = aorta; L = left; LMCA = left main coronary artery; PA = pulmonary artery; Post. = posterior; R = right.

tients, whereas evidence of regression was found in the remaining two. In one of the two patients with angiographic evidence of regression, the lesion remained prominent on echocardiography (Fig. 2 and 3). Six of seven patients with normal coronary echograms had normal coronary arteries on angiography. The remaining patient had a small aneurysm in the distal portion of the left anterior descending artery.

Thallium-201 myocardial scanning: Significant perfusion defects were not observed in serial follow-up studies that included eight patients with coronary lesions.

Cardiac catheterization data: In the patients who underwent catheterization, left ventricular end-diastolic pressure ranged from 8 to 18 mm Hg (mean 13) and ejection fraction 57 to 75 percent (average 64). No patient had evidence of left ventricular asynergy or mitral regurgitation.

Correlation of four cardiac indexes: There was a greater incidence of electrocardiographic changes (40.3 percent) than of M mode echocardiographic abnormalities (20.3 percent), cardiomegaly (20.3 percent) or gallop rhythm (12.7 percent) (Fig. 4, left panel). Eighty-one percent of patients with an abnormal echocardiogram, 75.0 percent of those with cardiomegaly and 90.0 percent of those with gallop rhythm had a coexisting abnormal electrocardiogram. Patients with abnormalities of more than one, two or three of the four cardiac indexes made up 50.6 percent (n = 40), 26.6 percent (n = 21) and 13.9 percent (n = 11) of the population, respectively, whereas abnormalities of all four indexes were present in only 5.1 percent (n = 4) (Fig. 4,

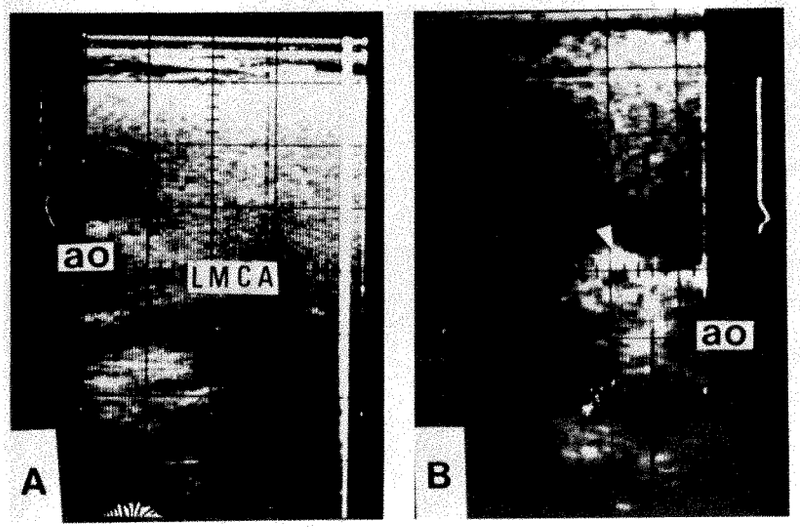

FIGURE 2. A, two dimensional echocardiograms taken 3 years after the onset of the disease, demonstrating regression of a left coronary arterial aneurysm. **B,** although an abnormal echo-free space noted in the stem of right coronary artery (**arrow**) also regressed, its outer wall became thickened and the overall size of the abnormal echo representing the aneurysm was similar to the initial echocardiogram (Fig. 4, Hiraishi et al.[24]). ao = aorta; LMCA = left main coronary artery.

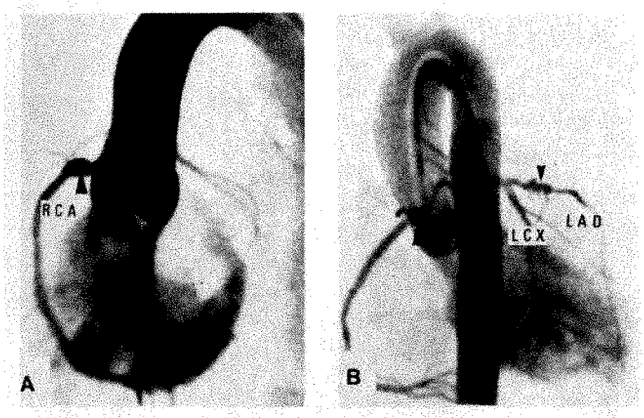

FIGURE 3. Aortograms (**A**, left oblique view; **B**, right oblique view) corresponding to the two dimensional echocardiograms in Figure 2. The regression of both the left and right coronary aneurysms (**arrows**) is observed. The **right arrow** in **B** demonstrates stenosis at the same location of aneurysm formation of the left anterior descending (LAD) coronary artery after 3 years. These angiograms should be compared with those of the initial evaluation (Fig. 4, Hiraishi et al.[24]). LCX = left circumflex coronary artery; RCA = right coronary artery.

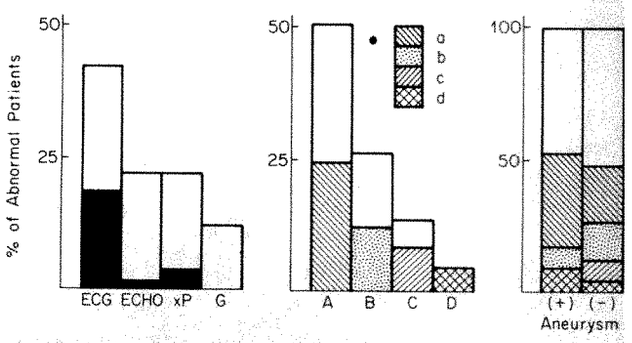

FIGURE 4. Left, percent of abnormal patients among all patients assessed by electrocardiogram (ECG), M mode echocardiography (ECHO), chest radiography (xP) and presence of gallop rhythm (G). **Shaded area** shows percent of patients with only one abnormality. **Middle,** percent of patients with abnormalities of one or more (A), two or more (B), three or more (C) and all four indexes (D). **Shaded areas** indicate percent of patients with abnormalities of one index (a) and two (b), three (c) and four (d) indexes. **Right,** comparison of the incidence of carditis among 11 patients with aneurysm (+) and 68 patients without aneurysm (−). The incidence of carditis is the same in the two groups. **Shaded areas** a, b, c and d are defined in the **middle** panel.

middle panel). Progression and regression of electrocardiographic abnormalities, especially of low amplitude R and T waves and S-T segment changes, correlated closely with progression of abnormal echocardiographic changes, cardiomegaly and gallop rhythm; that is, they appeared during stages I and II and were primarily resolved by stage III. In contrast, deep Q waves occurred in stages II and III and persisted in the later stages. Therefore, carditis was suspected when abnormalities of more than one of four cardiac indexes exclusive of Q waves existed. Because carditis consists of pericarditis, myocarditis and endocarditis, we further evaluated their frequency in this syndrome. Six of seven patients with pericardial effusion also had reduced fractional shortening. Pericardial effusion and reduced fractional shortening were echocardiographic features in the one patient who manifested a murmur of mitral regurgitation. Because these phenomena occurred in a single patient in stage I, pancarditis was very likely. It was therefore suggested that almost all patients with carditis had myocarditis.

Relation between carditis and coronary aneurysm: Six (54.5 percent) of 11 patients with coronary aneurysms had clinical evidence suggesting carditis, compared with 34 (50.0 percent) of 68 patients without coronary aneurysms (Fig. 4, right panel). Thus the frequency of carditis was the same in patients with and without aneurysms.

Other clinical data (Table II): The 79 patients studied were classified into four groups: Group A, 40 patients with carditis only; Group B, 7 patients with only a single coronary aneurysm; Group C, 4 patients with multiple coronary aneurysms; and Group D, 28 patients without significant clinical findings. No significant differences were found in any of the indexes evaluated among groups A, B and D. Group C, however, consisted of younger patients who had a prolonged period of increased erythrocyte sedimentation rate and elevated fever. Careful palpation of peripheral arteries, specifically the axillary and radial arteries, enabled the detection of axillary aneurysms and decreased pulsation of the radial artery in two patients in Group C. No significant difference was found in the duration and frequency of administration of aspirin and antibiotic therapy among the four groups. Corticosteroids were administered to six Group A and B patients with carditis in stages I and II, and three Group C patients

TABLE II
Clinical Data on 79 Patients

	Group A (40 patients)	Group B (7 patients)	Group C (4 patients)	Group D (28 patients)
Age				
Range	4 mo to 5 yr 10 mo	6 mo to 6 yr 9 mo	3 mo to 1 yr 3 mo	6 mo to 10 yr
Mean	2 yr 8 mo	2 yr 3 mo	8.8 mo	3 yr 1 mo
Mean duration of fever (days)	10.1	11.3	27	9.5
Mean duration of increased ESR (days)	27.8	37.5	56.3	22.0
Peripheral aneurysms in axillary artery	0	0	2 (50.0%)	0

ESR = erythrocyte sedimentation rate.

during stages III and IV. The duration of steroid therapy varied from 1 to 3 weeks.

Discussion

Carditis

Diagnostic criteria and incidence: Difficulty exists in making the diagnosis of carditis with reasonable reliability in current clinical practice.[15,28] In this study, 43 percent of all patients had electrocardiographic evidence of carditis. This is a rather low incidence rate in light of the electrocardiographic data presented by Asai,[12] which suggested that myocarditis or pericarditis, or both, occurred in almost all patients. Differences seem to be related to criteria utilized in making the electrocardiographic diagnosis. Our study excluded mild relative changes in R and T wave voltage because such changes may reflect fever or other related conditions. In our study, carditis was manifested not only by the electrocardiogram but also by the echocardiogram, the chest radiogram and the presence of gallop rhythm and a heart murmur. If carditis is defined by abnormalities of more than two or three of these four cardiac indexes, the specificity of the diagnosis is enhanced but mild cases with carditis might be overlooked because of a reduction in sensitivity. Of primary importance, serial changes of these findings corresponded. Moreover, we endeavored to correlate the clinical information with previously published pathologic data. In a pathologic report of 13 cases,[29] pericarditis, myocarditis and endocarditis were common in stages I through III in 100, 69 and 54 percent, respectively. Compared with the pathologic data, our clinical indexes showed a lesser incidence of carditis, especially pericarditis and endocarditis. These differences may be related to the sensitivity of the clinical indexes used and differences in populations studied. Of interest, the pathologic findings in patients with myocarditis correlated with the clinical stage.

Myocardial ischemia: A study of endomyocardial biopsies in this disease showed that myocardial changes may be due to ischemic changes caused by arteritis of small arteries.[30] In our echocardiographic studies, diminished septal motion without augmentation of left ventricular posterior wall motion was found in only four patients with carditis during stages I and II. Thallium-201 myocardial scanning showed no distinct decreased uptake. Therefore, it was difficult to detect significant myocardial ischemia in the early stage of the disease. In contrast, increasing deep Q waves without ST-T changes persisted from stage IV through stage V, in four patients, three of whom had coronary aneurysms. None of these patients had significant clinical findings other than abnormal Q waves. Although the most specific indicator of myocardial ischemia, primarily due to large coronary lesions in the active stage, was the presence of deep Q waves, their presence was not a sensitive indicator of aneurysm formation since they were observed in only 3 of 11 patients with aneurysms. Clinicopathologic studies[31] have demonstrated myocardial damage in more than 30 percent of the wall thickness of the left ventricle primarily due to myocardial infarction in patients with deep Q waves without associated ST-T changes. Our data revealed resolution of Q wave abnormalities during 2 years of follow-up study in three of the four patients.

Myocarditis: Our study suggests that abnormal clinical and laboratory findings occurring in stages I and II result from carditis, primarily myocarditis. Even in patients with large coronary lesions, significant clinical findings do not appear in these stages unless severe myocardial ischemia or myocardial infarction is present. To our knowledge, myocardial infarction has rarely been observed in these early stages,[32–34] and clinical and laboratory evidence of infarction such as sudden onset of vomiting, pallor, dyspnea, chest pain, abdominal pain, abnormal Q waves and ST-T changes were clearly different from the findings of myocarditis. However, large coronary lesions may occur in patients with an increased cardiothoracic ratio,[35] abnormal electrocardiogram (especially Q wave and ST-T changes),[36] echocardiographic evidence of reduced cardiac function, gallop rhythm or heart murmur,[37] especially when these findings occur after stage II.

Coronary Arterial Aneurysm

Coronary aneurysms were prospectively imaged with two dimensional echocardiography during stages II through III, primarily stage II. These findings concurred with the pathologic findings that large coronary arteritis occurred in stage I and large coronary aneurysms were observed in stage II.[29] Although coronary aneurysms were detected during stage III in three patients, we cannot be sure that these lesions occurred in stage III or were overlooked in stage II. In all 15 cases, two dimensional echocardiographic detection of the presence or absence of aneurysm of proximal portions of both the right and left coronary arteries correlated with angiographic data. The major limitation of two dimensional echocardiography in the diagnosis of coronary aneurysms was its inability to image the right coronary artery in 83 percent of our patients. Despite this limitation, large aneurysms of the right coronary artery (greater than 10 mm) were easily imaged.

Regression of coronary lesions and aneurysms: Angiographic studies[13,35] have confirmed that coronary aneurysms can either partially regress or completely disappear in stage V. Our serial two dimensional echocardiographic studies revealed that regression of coronary aneurysms may occur as early as stage III or IV. In these patients, angiographic evaluation was not performed in the active stages because it was considered dangerous. However, by stage IV or V when angiography was safe, two dimensional echocardiography was normal and angiography confirmed normal coronary anatomy. These data do not support previous angiographic reports[11,38] that demonstrated mild stenosis or arterial wall irregularities in stage IV or V. The difference may reflect our use of aortography rather than selective coronary angiography; however, this needs further study. Furthermore, serial echographic studies dem-

onstrated a thickening of the outer wall of the coronary aneurysm in one patient with angiographic evidence of regression. This information may indicate the pathologic process of aneurysm regression. In other words, aneurysm regression demonstrated angiographically does not imply complete recovery of the coronary artery but a reduction of its internal lumen due to some pathologic mechanism such as intimal thickening, granulation thrombi, scar formation or recanalization.[39]

Relation Between Carditis and Large Coronary Arterial Lesions

Panarteritis of large coronary arteries and inflammation of their vasa vasorum are suggested as important factors in the appearance of aneurysms.[39] However, this hypothesis has not been proved, and the relation between inflammation of myocardial microvessels and large coronary arteries has not been clarified. Our study showed that there was no distinct relation between coronary aneurysm formation and carditis, although it should be emphasized that carditis in this study is not a pathologic but a clinical diagnosis. No relation was found between the incidence and severity of carditis and the age of the patients. Conversely, severe coronary lesions were most often observed in infants. These patients had a longer period of elevation of the erythrocyte sedimentation rate and fever than the older patients. This age factor has previously been reported.[11,40] Therefore, we speculate that large coronary arteritis does not have direct continuity with inflammation of microvessels of the myocardium in stage I. The younger age group, primarily infants, may have either some anatomic weakness of the wall of a large coronary artery, as suggested by the report of Fujiwara et al.,[39] or a weak host defense mechanism such that severe inflammation is apt to occur in a large coronary artery, or both.

Acknowledgment

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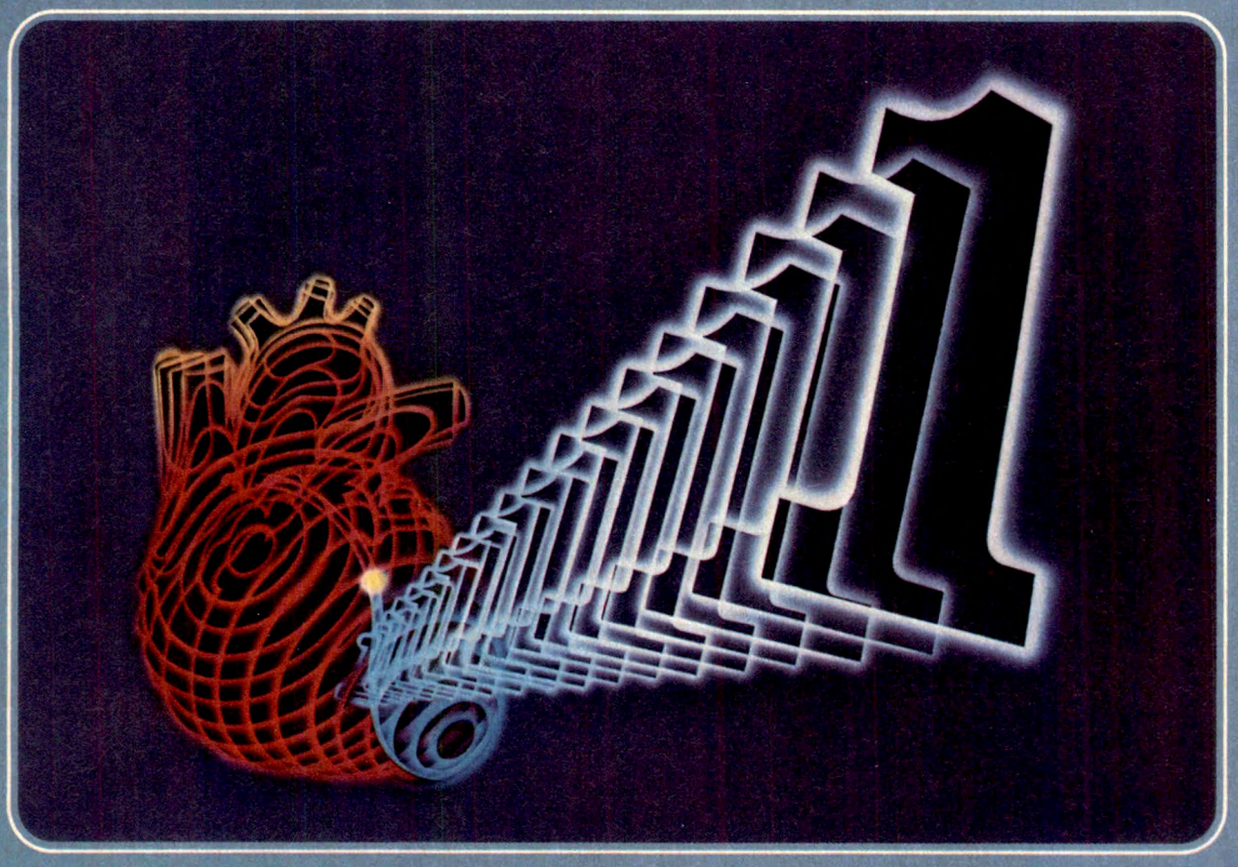

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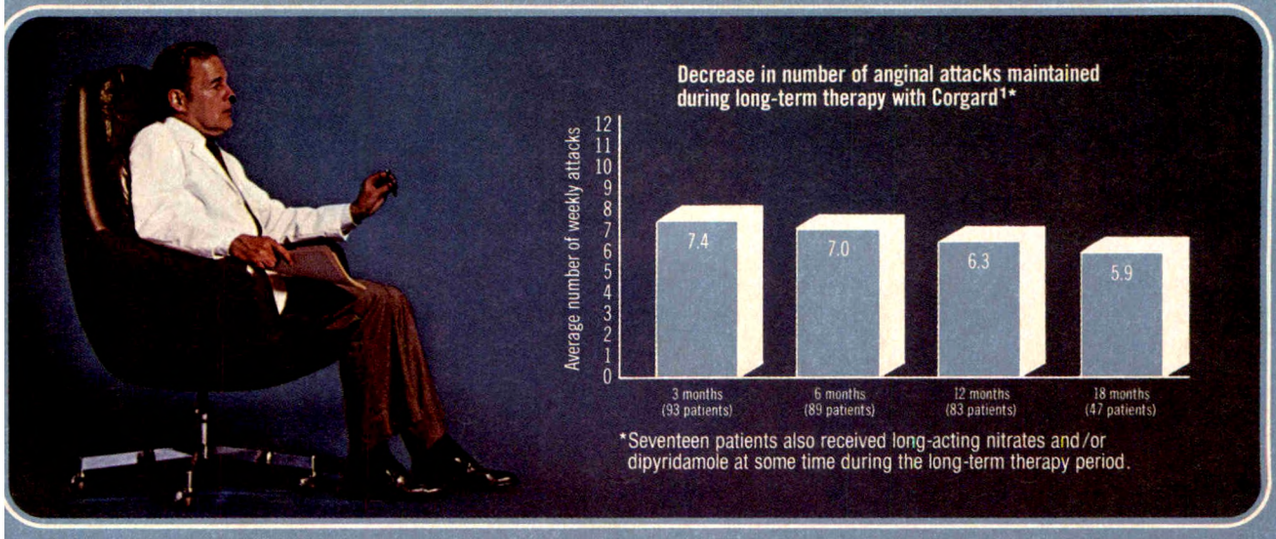

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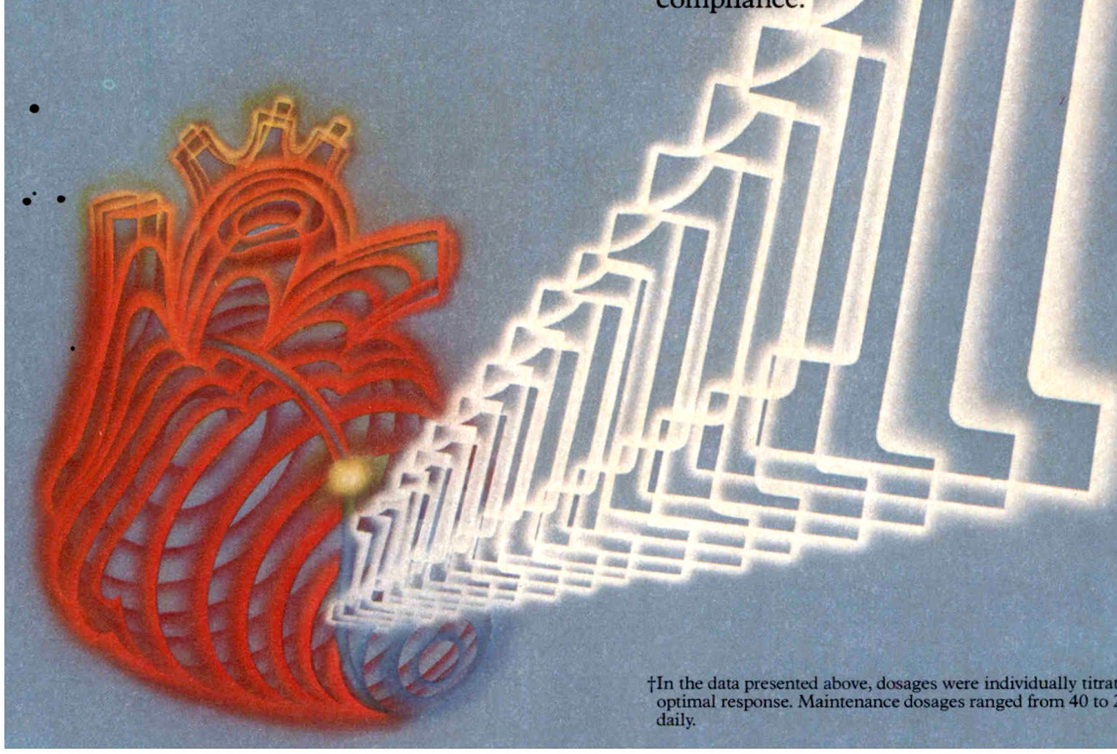
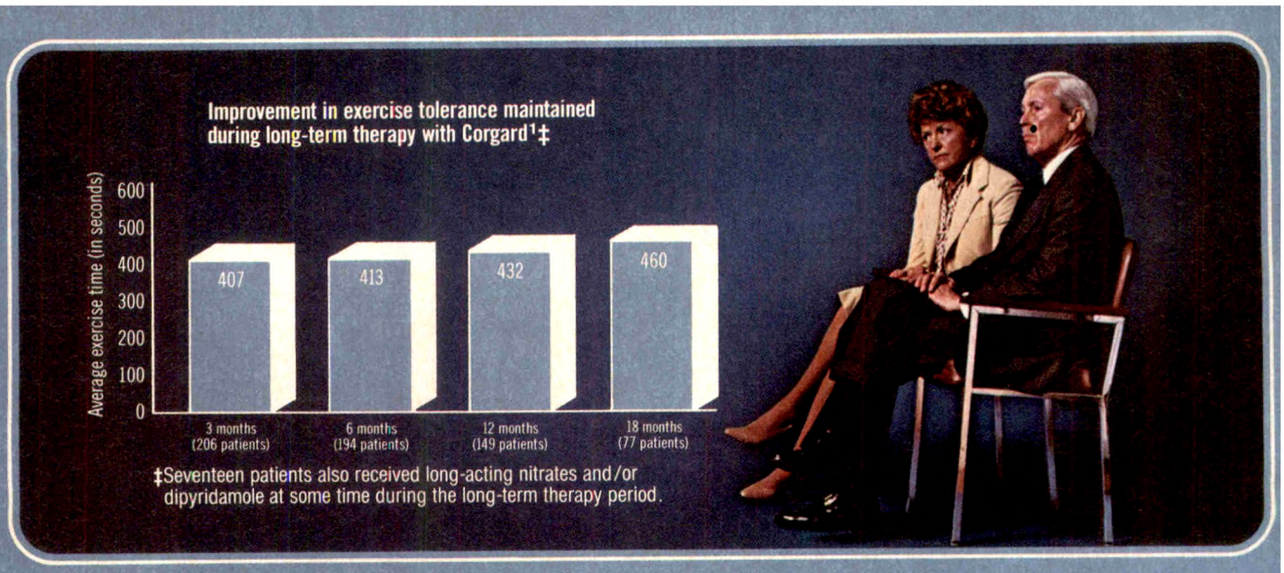


†In the data presented above, dosages were individually titrated to achieve optimal response. Maintenance dosages ranged from 40 to 240 mg Corgard daily.



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Corgard allows the angina patient to do more. In 147 patients in the same short-term study as the one at left, Corgard, once a day, increased ergometry time by 25%, improving exercise tolerance from an average of 365 seconds pretherapy to 427 seconds at the end of 14 weeks of therapy.[1] In 21% of the 147 patients, the end point of exercise was fatigue rather than angina pain. And the single daily dose of Corgard can be taken at the patient's convenience, without regard to meals.

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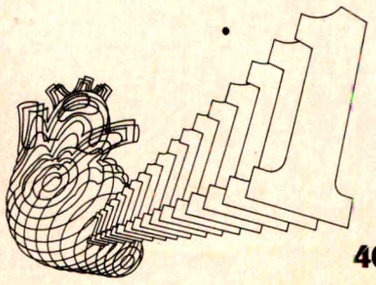

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

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1. Data on file, Squibb Institute for Medical Research.

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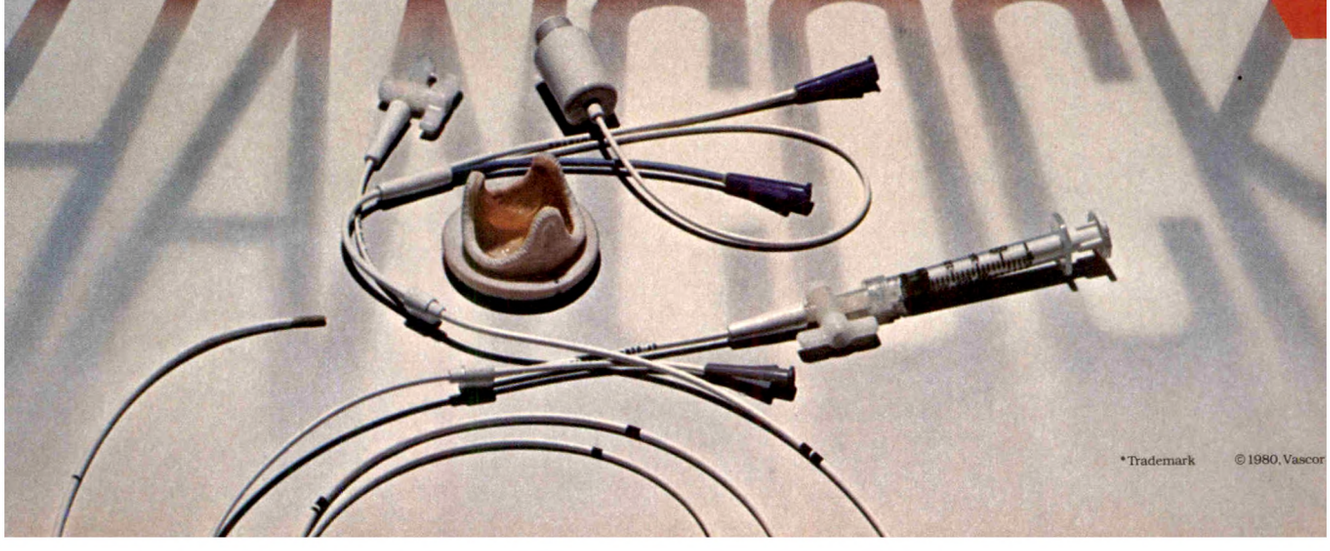

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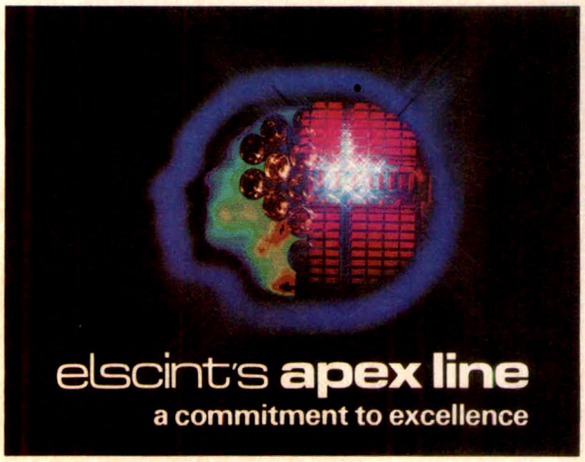

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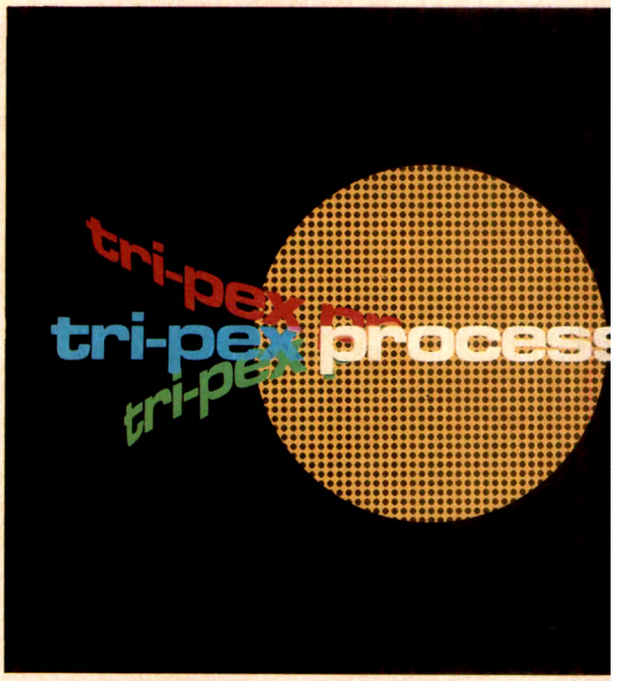

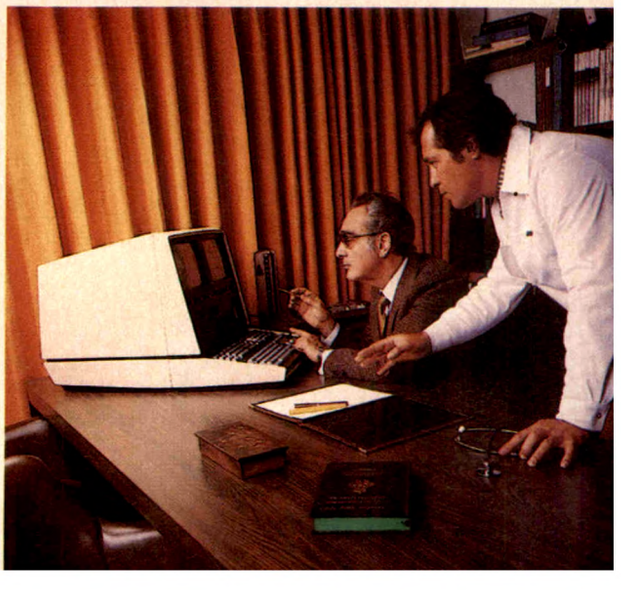

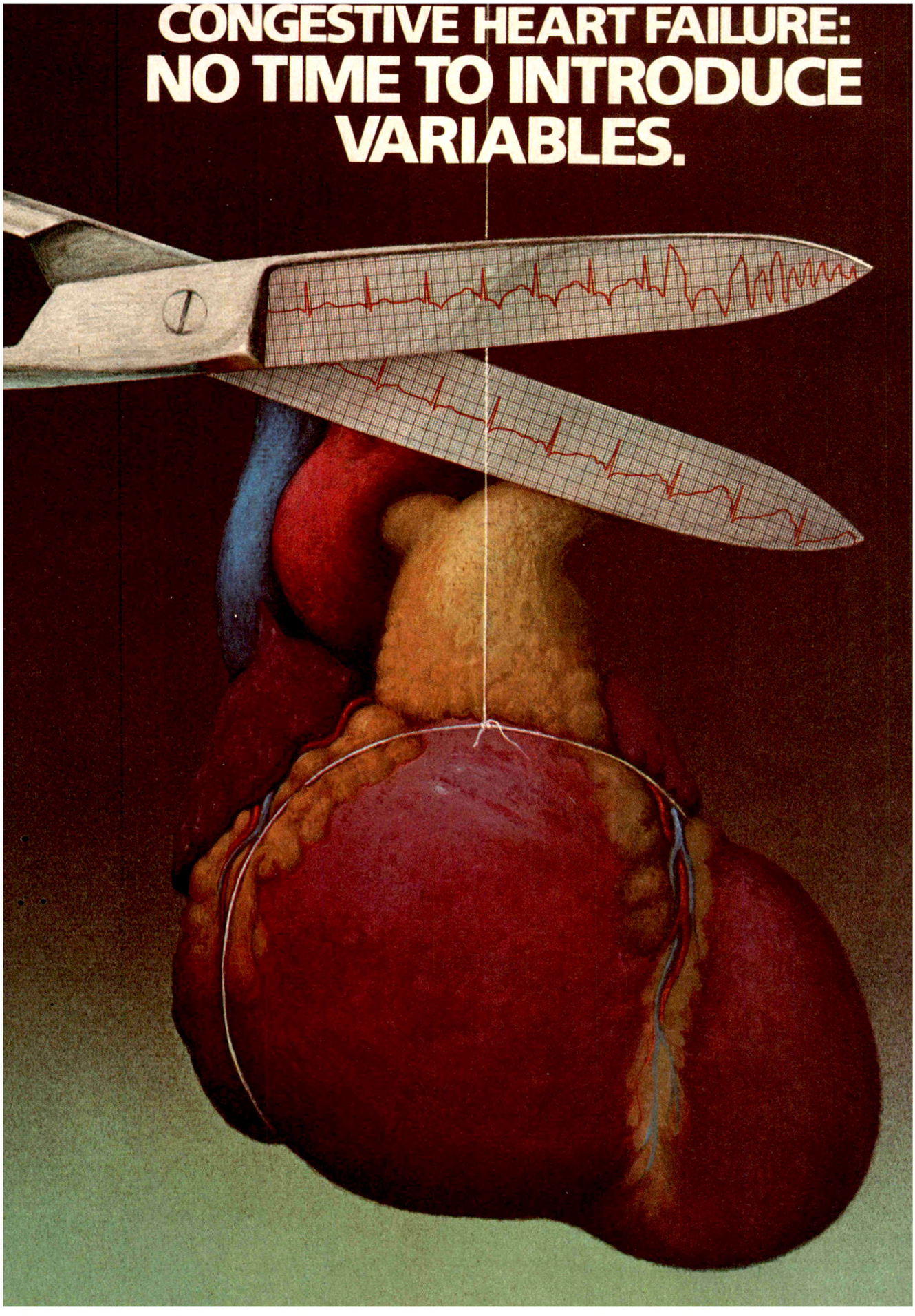
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IN CONGESTIVE HEART FAILURE.

LASIX®
FUROSEMIDE

ONE LESS VARIABLE IN THE DIGITALIZED PATIENT

Lasix® (furosemide)

A brief summary of the Prescribing Information for Lasix (furosemide). Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter, and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion: this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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Announcing the comprehensive study of...the most fascinating syndrome in Cardiology...

THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC

Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC

Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman of the Department of Medicine, The University of Alabama in Birmingham, and Physician-in-Chief, University of Alabama Hospitals.

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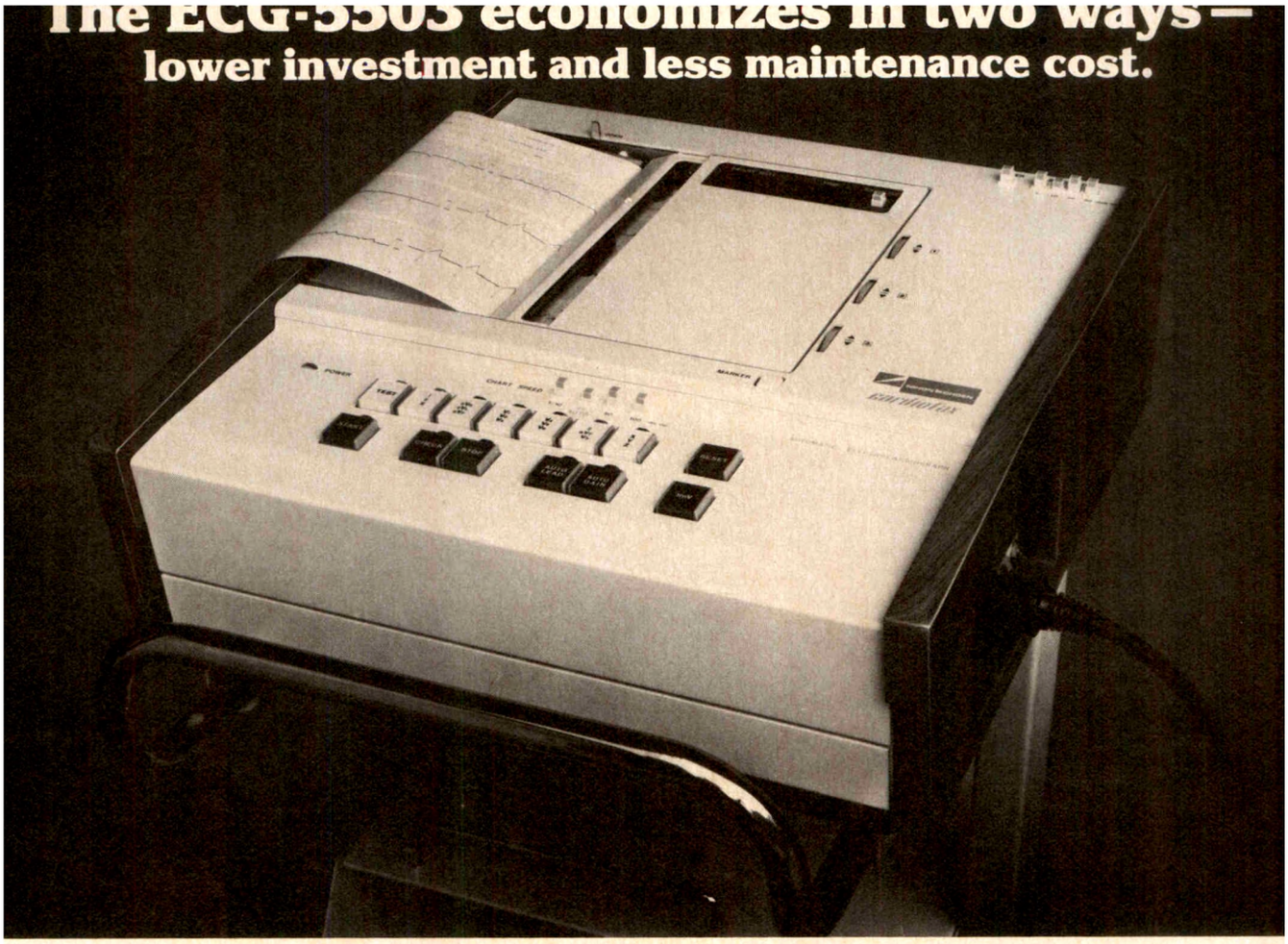

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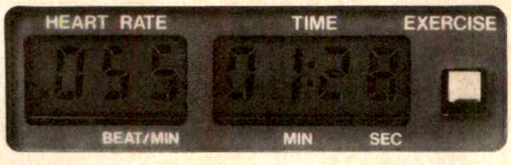

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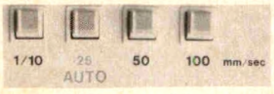

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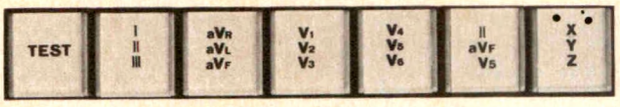

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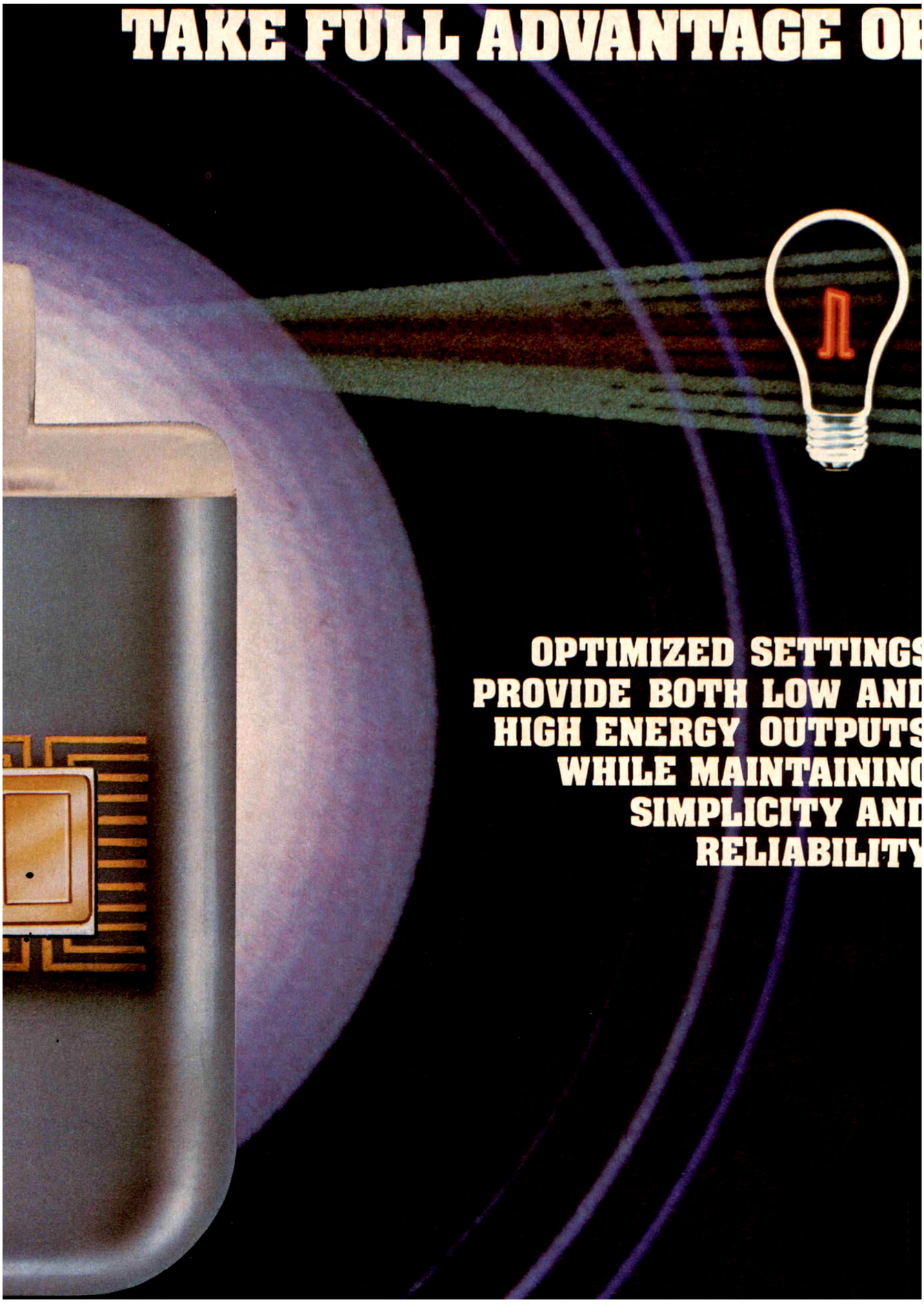
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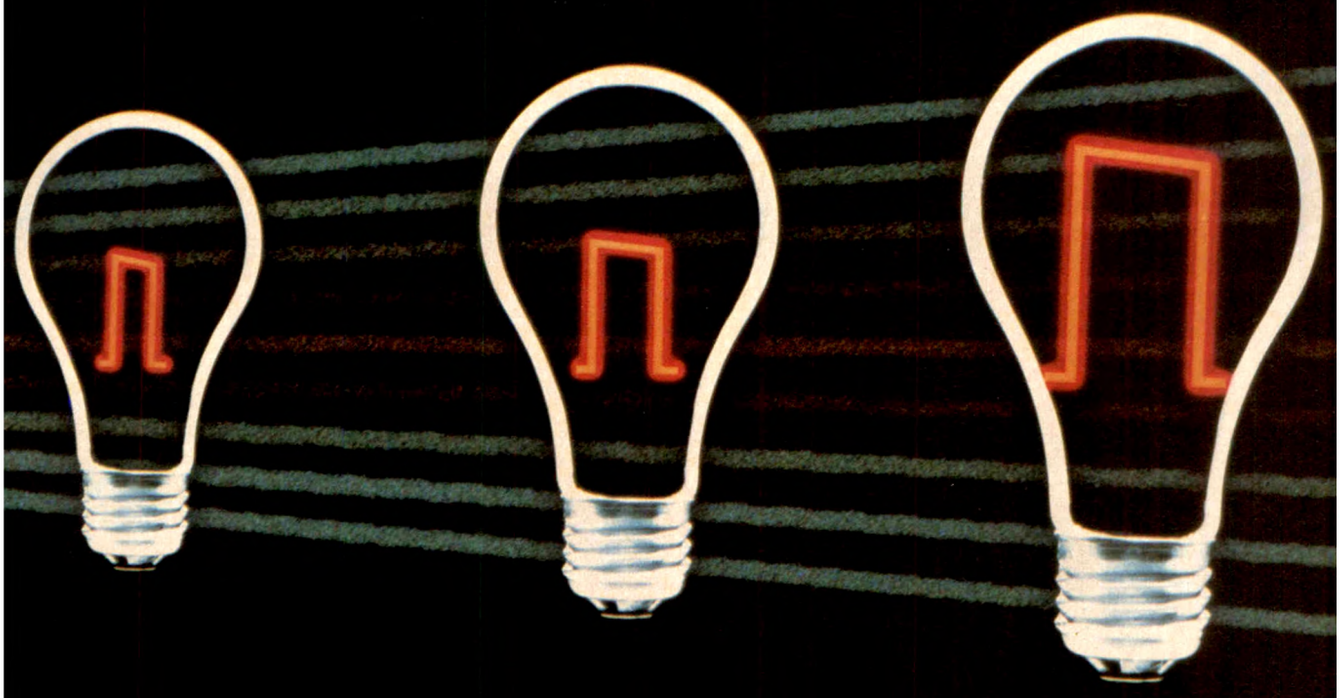

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REPORT OF THE JOINT NATIONAL
COMMITTEE ON DETECTION, EVALUATION
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NOW RECOMMENDED FOR INITIAL THERAPY IN SELECTED HYPERTENSIVE PATIENTS

"In selected younger patients with a rapid heart rate and/or high pulse pressure, beta-adrenergic blocking agents may be appropriate for Step 1 drug therapy."

—Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, 1980.

INDERAL®

(PROPRANOLOL HCl)

BID FOR HYPERTENSION

Please see following page for Brief Summary of Prescribing Information on Contraindications, Precautions, Adverse Reactions, and Warnings, including avoidance of abrupt withdrawal.

INDERAL®

(PROPRANOLOL HCl) B.I.D. FOR HYPERTENSION

BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® BRAND OF
propranolol hydrochloride
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

The mechanism of the antihypertensive effects of INDERAL has not been established. Among the factors that may be involved in the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain.

Propranolol hydrochloride decreases heart rate, cardiac output, and blood pressure. Although total peripheral vascular resistance may increase initially, it readjusts to the pretreatment level, or lower, with chronic usage. Earlier studies indicate that plasma volume remains unchanged or may decrease. However, there are certain more recent studies suggesting that in the absence of sodium restriction, plasma volume may increase.

INDICATIONS

Hypertension
INDERAL is indicated in the management of hypertension. It is usually used in combination with other drugs, particularly a thiazide diuretic. INDERAL is not indicated for treatment of hypertensive emergencies.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of [illegible] INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effect can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especiall important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been estab lished. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximur recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with achin and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

ORAL

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 40 mg INDERAL twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure is achieved. The usual dosage is 160 to 480 mg pe day. In some instances a dosage of 640 mg may be required. The time needed for full hyper tensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12 hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3 times daily therapy may achieve better control.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE I EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE).

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

INDERAL
(propranolol hydrochloride)

TABLETS

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCE

Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,: Arch. Intern. Med. *140*:1280 (Oct) 1980.

7514/18

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Platelet Function in Hypertension and Effect of Therapy

JAWAHAR MEHTA, MD, FACC
PAULETTE MEHTA, MD

Gainesville, Florida

Platelet function was evaluated in 10 hypertensive and 11 normal subjects. In the placebo phase, the plasma beta thromboglobulin level (an index of platelet activation in vivo) was significantly ($p < 0.01$) higher in the hypertensive than in the normal subjects; other tests of platelet function gave similar results in the two groups. After control of blood pressure with lofexidine (a centrally acting imidazoline derivative), plasma beta thromboglobulin levels decreased in 9 of the 10 hypertensive patients, but increased in one who showed no change in blood pressure. These studies suggest that enhanced platelet activation in primary hypertension may be associated with increased vascular resistance.

Platelet dysfunction has been observed in several vascular disorders.[1–4] An increase in in vivo platelet aggregation may lead to impeded blood flow[5] and subsequent manifestations of tissue ischemia such as myocardial infarction[6,7] and cerebrovascular accidents.[3,8] Recently, it was proposed[9] that enhanced formation of platelet aggregates in the peripheral vessels may be a mechanism of increased vascular resistance. Platelet aggregation inhibitory effects of certain pharmacologic agents that decrease vascular resistance may in part be a mechanism of their beneficial action.[9,10] Poplawski et al.[11] demonstrated increased platelet adhesiveness in hypertensive subjects. In other studies,[12,13] in vitro platelet aggregation was also increased in hypertensive compared with normal subjects. The present study was conducted in a select group of hypertensive subjects to examine further different variables of platelet function in hypertension. The effects of antihypertensive therapy on alterations in platelet function were also evaluated.

Methods

Study subjects: Ten men aged 24 to 67 years (mean 50 ± 5) with documented primary hypertension of 6 months' to 4 years' duration were studied. The patients were included only if diastolic blood pressure was over 90 mm Hg on multiple examinations after discontinuation of any previous treatment with antihypertensive medications or diuretic drugs, or both, for at least 2 weeks. During this period, the patients were given a placebo capsule containing no active medication and followed up to document the presence of hypertension (placebo phase). Patients with clinical evidence of vascular disease, diabetes mellitus, gout or renal, hepatic or pulmonary dysfunction were excluded from the study. Particular attention was given to evaluation of renal function, because impaired renal function may affect certain variables of platelet function.[14] All patients gave informed consent before entering the study. The patients were asked not to take any platelet-active drug or diuretic agent during the placebo phase or subsequent drug study period.

After *documentation of hypertension*, each patient was started on treatment with lofexidine, a centrally acting imidazoline derivative antihypertensive agent,[15–17] 0.1 mg twice daily. The patients were followed up each week for control of blood pressure. The dose of medication was increased to a maximum of 0.3 mg twice daily to achieve adequate control of blood pressure (drug study phase).

From the Divisions of Cardiology and Hematology/Oncology, Departments of Medicine and Pediatrics, University of Florida, Shands Teaching Hospital and Veterans Administration Medical Center, Gainesville, Florida. This study was supported in part by the American Heart Association, Florida Affiliate, Palm Beach County Chapter, West Palm Beach, Florida, and by Merrell Research Laboratories, Cincinnati, Ohio. Manuscript received May 27, 1980; revised manuscript received August 26, 1980, accepted September 9, 1980.

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Platelet function studies were also performed on one occasion in 11 other age- and sex-matched normal subjects. No normal subject had taken a platelet-active drug in the preceding 2 weeks.

Platelet studies: Platelet studies performed in the hypertensive patients included quantitation of aggregation responses to epinephrine and adenosine diphosphate (ADP) by light transmission as described previously.[4,18] Circulating platelet aggregates were evaluated by the method of Wu and Hoak.[1] Platelet sizing was done using an optical linear micrometer on 500 cells.[19] Platelet counts were done by phase microscopy after lysis of red cells with procaine hydrochloride.[20]

Plasma beta thromboglobulin assay was performed by radioimmunoassay.[2,21,22] Whole blood (2.5 ml) was collected using a 20 gauge, 1 inch (2.5 cm) needle and polystyrene syringe. A good venipuncture with freely flowing blood was obtained. Immediately after collection the needle was removed from the syringe and blood transferred gently to a precooled labeled sampling tube supplied with the kit. The tube was inverted three times and immediately cooled by placing it in a rack in a cooling bath. The sample was centrifuged at 4° C for 30 minutes. Centrifugation was carried out within 1 hour after collection. After centrifugation the top 0.5 ml was pipetted with a disposable plastic tip into a separately labeled specimen tube. The sample was stored at −20° C for a maximum of 3 weeks. Samples were thawed and mixed well before use. Aliquots of 50 μliter of reconstituted standards and of patient blood samples were pipetted into assay tubes. Aliquots of 200 μliter of beta thromboglobulin–iodine-125 solution and of 200 μliter of anti–beta thromboglobulin serum solution were mixed and whirled in the tubes. The tubes were incubated at room temperature for 1 hour. Ammonium sulfate solution (500 μliter aliquots) was added to each of the assay tubes, after which the tubes were spun. Tubes were centrifuged for 15 minutes at 1000 *g*; they were then removed from the centrifuge and placed in decantation racks, and supernatant liquids were discarded. The precipitate remained undisturbed during this procedure. After draining of supernatant material, the precipitates were counted in a gamma counter. The concentration of beta thromboglobulin (ng/ml) was determined from a standard curve established from readings of radioactivity counts/second obtained from known samples with the kit.

These platelet studies were done during the placebo and the drug study phases in all patients. In all but one patient, the second set of platelet function studies were performed at the dose of lofexidine necessary for control of blood pressure. In one patient, blood pressure could not be controlled with the maximal dose of lofexidine, and platelet function studies were done while he was taking 0.6 mg of lofexidine per day.

Calculations: The data are expressed as mean ± standard error of the mean. Student's *t* test (paired and unpaired data) was used for statistical calculations. A p value less than 0.05 was considered significant.

TABLE I

Platelet Studies in Normal and Hypertensive Subjects

	Normal Subjects	Hypertensive Subjects	
		Placebo Phase	Drug Study Phase
Platelet counts (per mm^3)	275,000 ± 41,000	290,000 ± 32,000	257,000 ± 21,000
Platelet size (μ)	2.12 ± 0.04	2.0 ± 0.02	2.01 ± 0.03
Platelet aggregation (%)			
Epinephrine	72 ± 7	62 ± 11	66 ± 11
Adenosine diphosphate	70 ± 5	74 ± 4	75 ± 4
Circulating platelet aggregates (%)	7 ± 2	9 ± 3	8 ± 2
Plasma beta thromboglobulin (ng/ml)	42 ± 5	108 ± 21*	66 ± 10†

* $p < 0.01$, hypertensive subjects in placebo phase compared with normal subjects. † $p < 0.05$, hypertensive subjects in drug study phase compared with placebo phase.

Results

Blood pressure and heart rate: In the placebo phase, blood pressure in the hypertensive patients was 144 ± 4/96 ± 1 mm Hg (systolic/diastolic) in the sitting position. The heart rate was 76 ± 3 beats/min. After 2 to 6 weeks (mean 3 ± 1 week) of therapy with lofexidine (mean dose 0.5 ± 0.1 mg/day), blood pressure in the entire group of patients had gradually decreased to 122 ± 4/84 ± 2 mm Hg ($p < 0.001$ compared with the placebo phase). Heart rate was unchanged at 71 ± 3 beats/min (difference not significant [NS]). Blood pressure was uncontrolled in one patient at the maximal dose of lofexidine.

Platelet studies: Results of the platelet function studies in normal and hypertensive subjects are summarized in Table I. Platelet counts and size were similar in the two groups. Platelet aggregation in response to the addition of epinephrine and ADP in hypertensive patients was comparable with that in the normal subjects. Circulating platelet aggregates were in the normal range in all but one of the hypertensive patients, but the mean values were similar to those in the normal subjects.

Plasma beta thromboglobulin levels ranged from 21 to 230 ng/ml (mean 108 ± 21) in hypertensive patients compared with 42 ± 5 ng/ml (range 35 to 55) in the normal subjects. This difference was statistically significant ($p < 0.01$). Of the 10 hypertensive patients, 7 had a beta thromboglobulin level 2 standard deviations or more above the normal range, whereas 3 had a level in the normal range. The plasma beta thromboglobulin level did not correlate with blood pressure or with degree of platelet aggregation, platelet counts or size. Nevertheless, one patient with abnormally high circulating platelet aggregates (27 percent) had a very high level of plasma beta thromboglobulin (230 ng/ml).

With therapy, platelet counts increased in three patients and decreased in seven, but the change was not significant. Similarly, platelet size was not altered by drug therapy. Maximal platelet aggregation in response to epinephrine and ADP and circulating platelet aggregates were not affected by lofexidine therapy. After treatment with lofexidine, the plasma beta thromboglobulin level decreased ($p < 0.05$) in all but one patient (Fig. 1). The patient whose beta thromboglobulin level increased (from 77 to 129 ng/ml) had no change in blood pressure. The decrease in plasma beta thromboglobulin

level was most marked in the patients with the highest values in the placebo phase, whereas those with minimal elevation of beta thromboglobulin levels had only a slight decrease. There was no correlation between change in blood pressure and plasma beta thromboglobulin level.

Effect of lofexidine on renal function: In the placebo phase, blood urea nitrogen (range 10 to 23 mg/100 ml, mean 15 ± 3) and serum creatinine (range 0.3 to 1.2 mg/100 ml, mean 0.7 ± 0.1) were within the normal range in all study patients. With therapy, no significant changes occurred either in blood urea nitrogen (range 9 to 25 mg/100 ml, mean 14 ± 3) or in serum creatinine (range 0.6 to 1.1, mean 0.8 ± 0.1). Similarly, serum electrolytes were unaffected by lofexidine therapy. Urinalysis in the placebo and drug study phases revealed no evidence of a significant effect of lofexidine on renal function.

Discussion

The results of this study show that plasma beta thromboglobulin levels are significantly increased in certain patients with hypertension. All other variables of platelet function such as aggregation responses to epinephrine and ADP, circulating platelet aggregates and platelet counts and size are within the normal range.

Plasma beta thromboglobulin in hypertension: This secretory product of platelets is released by their alpha granules during the release reaction. In several studies,[2,23] plasma beta thromboglobulin levels were correlated with the state of platelet activation and survival in vivo. In another study,[22] plasma beta thromboglobulin levels and platelet factor 4 were found to be increased, indicating platelet activation in a select group of patients with vascular disease. A close correlation between the two tests of platelet function was found. In contrast, in vitro platelet aggregation and in vivo circulating platelet aggregates have produced variable indexes of platelet activation in states of vascular disease.[24,25] Platelet counts and size provide a crude index of platelet kinetics and activation.

In the present study, we chose a small but select group of patients who had not taken any platelet-active or antihypertensive agent during the preceding 2 weeks. Blood pressure in each of the subjects was clearly abnormally increased and there was no evidence of renal impairment. A state of enhanced in vivo platelet activation as reflected by an increase in the plasma beta thromboglobulin level in 7 of 10 patients suggests a relation between platelets and blood pressure. Previous studies have shown increased platelet adhesiveness[11] and platelet aggregation[13,14] in hypertensive patients. However, the results of tests of platelet adhesion may vary, and the method itself may not be very reproducible.[26] Nevertheless, elevated levels of plasma beta thromboglobulin may indicate platelet activation in the hypertensive state which may not be detected by other laboratory tests of platelet function. Whether platelet activation is a cause of increased resistance or a result

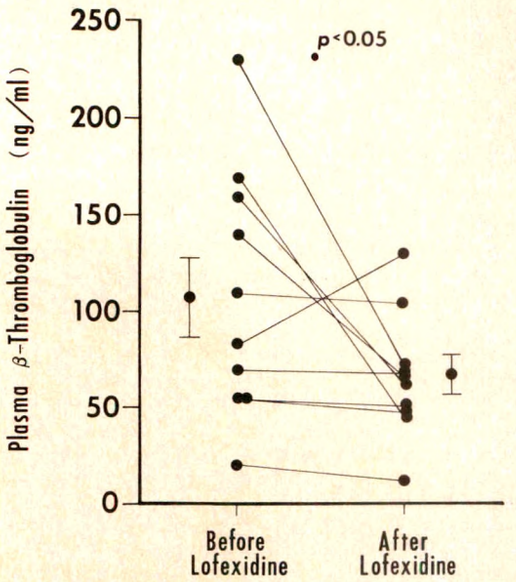

FIGURE 1. Effect of antihypertensive therapy on plasma beta thromboglobulin levels in 10 hypertensive patients.

of abnormal vascular tone in these patients is not clear from this study. Increased catecholamines in primary hypertension as documented by Vlachakis and Aledort[12] could account for enhanced platelet release reaction, but circulating catecholamine levels even in pathologic situations are not usually high enough to induce aggregation in themselves. However, they may contribute to the potentiation of aggregation and release reaction.

Antihypertensive agents and platelets: Several drugs used in the treatment of hypertension, such as phentolamine, propranolol and nitroprusside, have platelet aggregation inhibitory effects.[27–29] Lofexidine's major antihypertensive action is at the level of the central nervous system.[15–17] Lofexidine produces biochemical changes consistent with a central sympathomimetic effect.[30] In one study, epinephrine-induced platelet aggregation was inhibited by lofexidine,[31] implying its actions on platelet alpha$_2$ adrenergic receptors. In our patients, we found no specific alteration in circulating platelet aggregates or aggregation responses to epinephrine and ADP during therapy with lofexidine. However, this plasma beta thromboglobulin level decreased as blood pressure was controlled with lofexidine, although in one patient the plasma level increased while blood pressure was unchanged. It is not clear whether the decrease in plasma beta thromboglobulin level was due to a decrease in blood pressure or was directly related to lofexidine. It is conceivable that modulation of alpha adrenergic receptors with lofexidine results in a decrease in platelet activation and subsequently normal platelet release reaction. Although we did not measure the circulating catecholamines, it is possible that a decrease in plasma catecholamines may have been responsible for changes in plasma beta

ıromboglobulin levels. In several other studies,[13,32,33] lasma catecholamines were reported to increase after ıerapy of hypertension. Whether a similar phenomeon occurs with lofexidine as well is not known.

Clinical implications: Our observations suggest that latelet activation may be related to the hypertensive ;ate. Further studies are needed to determine whether ıhibition of platelet activation with platelet-suppressive agents ameliorates some of the clinical sequelae ı patients with hypertension. A recent report[34] suggests ıat modulation of platelet function and prostaglandin pathways by drugs like indomethacin may alter activity of potent antihypertensive agents such as hydralazine. Measuring the plasma beta thromboglobulin level in patients with hypertension as a means of assessing platelet contribution provides an avenue for further studies in this area.

Acknowledgment

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Clinical Correlates in Hypertensive Patients With Left Ventricular Hypertrophy Diagnosed With Echocardiography

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Seventy-three hypertensive patients were evaluated with M mode and two dimensional echocardiography. Left ventricular hypertrophy was found in 37 patients (51 percent); 29 had concentric hypertrophy and the remaining 8 had disproportionate septal thickening. Factors that did not influence the distribution of patients in the group with left ventricular hypertrophy and normal subjects included (1) duration of hypertension, (2) level of blood pressure, (3) age, (4) body surface area, and (5) race. More of the patients who had a normal left ventricular mass (32 or 89 percent) than of those who had hypertrophy (22 or 59 percent) were receiving two or more antihypertensive drugs. Electrocardiography was very insensitive in identifying left ventricular hypertrophy in these patients. The presence of increased left ventricular mass was associated with a greater incidence of other target organ disease.

The importance of determining left ventricular size and performance in patients with systemic hypertension is well recognized by clinicians. Significant cardiac manifestations of target organ involvement secondary to hypertension include myocardial infarction, left ventricular hypertrophy and left ventricular dysfunction. Traditionally electrocardiography has been considered a reliable method and a more sensitive tool than chest roentgenography to detect left ventricular hypertrophy.[1,2]

In recent years the application of M mode echocardiography has proved the most reliable method for measuring left ventricular wall thickness and function in hypertensive patients.[3–10] However, its application has been restricted by the inherent limitations of the M mode single dimension method. Furthermore, it is difficult to interpret the effects of hypertension on wall thickness or left ventricular function without first excluding wall motion abnormalities caused by previous myocardial infarction.

Although cardiac hypertrophy is one of the fundamental mechanisms of adaptation to abnormal loading conditions, studies on the effects of hypertrophy on myocardial performance are controversial. Sasayama et al.[11] found that the linear relation between left ventricular diameter and wall stress at the end of ejection was the same in control and hypertrophied dog hearts. These investigators concluded that in successful adaptation to the pressure overload, hypertrophy did not produce intrinsic depression of the myocardial inotropic state. Takahashi et al.[12] reported that myocardial contractility may be depressed in hypertensive patients with advanced left ventricular hypertrophy; in seven patients the end-systolic wall stress-diameter relation was shifted to the right. Karliner et al.[6] concluded that the hypertrophic response to a chronic increase in systemic arterial pressure did not result in depression of the basal inotropic state of the left ventricle.

This study was undertaken to investigate the cardiac manifestations of essential hypertension by M mode and two dimensional echocardiography with special reference to left ventricular anatomy and function and to correlate these findings with the other clinical features and target organ involvement.

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Methods

Study patients: The study group consisted of 82 patients who were referred from a hypertension clinic where clinical evaluation and therapeutic control of elevated blood pressure had been accomplished. The population was unselected except that patients with evidence of previous myocardial infarction, valvular heart disease or cardiomyopathy were excluded. Furthermore, only patients who had technically satisfactory M mode and two dimensional echocardiograms were included. The final study group comprised 73 patients, 35 men and 38 women ranging in age from 28 to 85 years (mean 57). All except two patients were receiving antihypertensive treatment at the time of the study. History, physical examination, electrocardiography and determination of serum electrolytes and creatinine were conducted on the same day that echocardiography was performed.

Echocardiographic studies: Combined M mode and two dimensional echocardiographic studies were performed with a Varian V-3000 wide angle, phased array system (Varian Associates, Palo Alto, California) interfaced with a Sanyo 7100 videotape recorder. All patients were positioned in a 30° left lateral decubitus position with slight elevation of the head. Comprehensive two dimensional tomographic planes were employed with multiple parasternal views of the left ventricle in long and short axes, apical four chamber and long axis views, and subcostal four chamber and short axis views. After positioning of the cursor through the interventricular septum and posterior wall at the level of the chordae tendineae, simultaneous M mode and two dimensional recordings were obtained from the parasternal transducer position in both long and short axis views of the left ventricle (Fig. 1). All views were carefully evaluated by at least two observers for evidence of any regional wall motion abnormality to be certain that all patients with previous myocardial infarction were excluded from the study. Four patients were excluded because the two dimensional studies were technically inadequate to make accurate wall thickness measurements. M mode or two dimensional echographic studies, or both, were utilized in the remaining 73 patients to determine the thickness of the interventricular septum, posterior left ventricular wall, cross-sectional area of the left ventricle and percent fractional shortening.

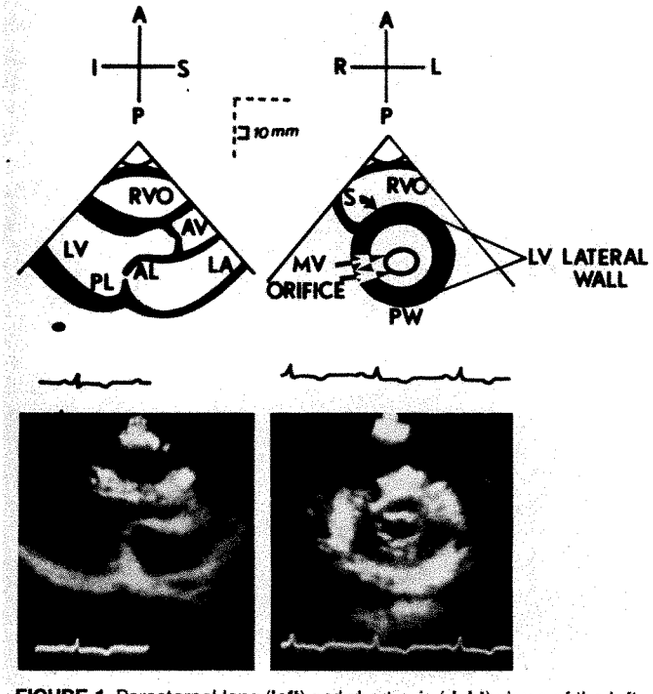

FIGURE 1. Parasternal long (**left**) and short axis (**right**) views of the left ventricle (LV). Although multiple views of the left ventricle were obtained with two dimensional echocardiographic imaging, these two tomographic planes were the most reliable for recording M mode studies at the tips of the mitral leaflets or through the chordae tendineae. A = anterior; AL = anterior mitral leaflet; AV = aortic valve; I = inferior; L = left; LA = left atrium; MV = mitral valve; P = posterior; PL = posterior mitral leaflet; PW = posterior wall of the left ventricle; R = right; RVO = right ventricular outflow tract; S = septum and superior.

Echocardiographic measurements: The left ventricular posterior wall and septum were measured at the time of atrial depolarization before the onset of the *a* notch. The end-diastolic dimension (EDD) of the left ventricle was determined at the level of the chordae tendineae at the peak of the R wave from the electrocardiogram, and the end-systolic dimension (ESD) was measured at the minimal cavity diameter from the same beat. M mode measurements were taken by the leading edge to leading edge technique as recommended by the American Society of Echocardiography. All measurements were averaged to the closest 1 mm from three good quality cardiac cycles. All M mode and two dimensional studies were interpreted simultaneously by two investigators (A.D.H. and A.C.) without knowledge of the patients' clinical information. Whenever discordance exceeded 1 mm between M mode and two dimensional measurments, the two dimensional study was used as a quality control check on the accuracy of the M mode calculations. The loss of endocardial reflectances from both the septum and the posterior wall may contribute to underestimating the respective wall thicknesses without the additional use of two dimensional imaging (Fig. 2).

Calculations from echocardiographic measurements were: (1) percent fractional shortening (% FS) = [(EDD − ESD)/EDD] × 100, and (2) cross-sectional area (CSA) in square centimeters, calculated as an index of left ventricular mass[13] as follows: $CSA = \pi [(EDD + S_D + PW_D)/2] - \pi [(EDD/2)^2]$, where S_D = diastolic thickness of the ventricular septum and PW_D = diastolic thickness of the posterior wall of the left ventricle.

Normal criteria for left ventricular measurements and derived calculations were as follows: (1) S_D and PW_D, 11 mm or less; (2) CSA, 21 cm^2 or less; (3) EDD, 54 to 57 mm or less depending on body surface area; and (4) % FS, 31 or greater.

Clinical features and groups: In addition to the echocardiographic and laboratory studies, the following clinical information was also recorded: (1) duration of hypertension (less than 5 years, 5 to 15 years, or greater than 15 years); (2) number, type and dosage of antihypertensive drugs; (3) standard cuff blood pressure; (4) history of stroke or recurrent transient cerebral ischemia; and (5) fundoscopic findings, graded 0 to IV using standard criteria for hypertensive retinopathy.

The 73 patients were classified into two groups: Group I included patients with a normal left ventricular wall thickness, that is, a posterior wall thickness of 11 mm or less; and Group II included those with left ventricular hypertrophy, that is, a posterior wall thickness of 12 mm or greater.

Results

Left ventricular hypertrophy: Of the 73 patients studied, 37 (51 percent) had left ventricular hypertrophy with a mean thickness of the posterior wall and interventricular septum of 13.4 and 14.2 mm, respectively (Table I). Twenty-nine of these patients had

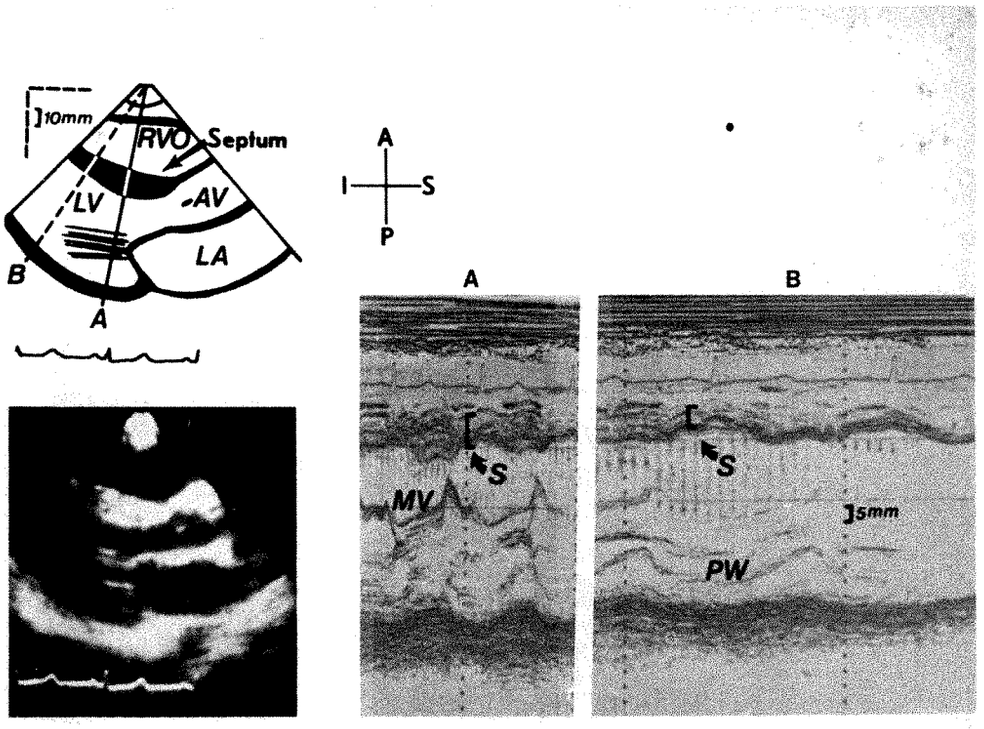

FIGURE 2. Two-dimensional echocardiogram in parasternal left ventricular (LV) long axis view (**left**) with corresponding M mode echocardiogram (**right**) showing the M mode cursor intersecting the septum at two different levels. The M mode recording at the tip of the mitral leaflets (**A**) reveals the correct thickness of the septum; the M mode recording in **B** demonstrates the apparent thickness of the septum to be much thinner due to echographic "dropout" of the reflectances from the right side. Abbreviations as in Figure 1.

concentric hypertrophy and 8 had disproportionate septal thickening. Group I consisted of 36 patients (49 percent) with a normal wall thickness; in this group the mean thickness of the posterior wall and interventricular septum was 9.9 and 10.5 mm, respectively. A significant difference existed in left ventricular mass as determined by cross-sectional area measurements of the left ventricle in the two groups: 16.4 ± 2.6 cm^2 in Group I versus 26.8 ± 3.2 cm^2 in Group II ($p < 0.01$) (Table I, Fig. 2).

There was no significant difference in age, body surface area or race in the two groups (Table II). However, there was a significantly greater proportion of women in Group I (20 versus 16) and a greater proportion of men in Group II (26 versus 11) ($p < 0.05$).

Blood pressure: Most of the patients demonstrated satisfactory control of blood pressure with the antihypertensive therapy being administered at the time of the study. Furthermore, no significant difference in blood pressure existed in the normal subjects in Group I and the group with left ventricular hypertrophy; mean blood pressure in Group I was 142/87 ± 15/11 mm Hg compared with 154/88 ± 26/24 in Group II (Table II). Seven (19 percent) of the 36 patients without left ventricular hypertrophy and 12 (32 percent) of the 37 patients with hypertrophy had a blood pressure of 160/90 mm Hg or greater.

Duration of hypertension: The duration of hypertension did not influence the distribution of patients in the two groups. In contrast to findings reported by Ross et al.,[7] no significant difference was found in the two groups when the patients were classified on the basis of the duration of hypertension (Table II). A history of hypertension longer than 5 years existed in 24 (67 percent) of the 36 normal patients in Group I and in 27 (73 percent) of the 37 patients in Group II. Of the 37 patients with left ventricular hypertrophy, 27 had had hypertension for more than 5 years and 10 for less than 5 years.

Treatment: Although longer duration of hypertension was not associated with a greater incidence of left ventricular hypertrophy, a significantly greater proportion of the normal subjects in Group I (32 of 36 or 89 percent) than of patients in Group II (22 of 37 or 59 percent) were receiving two or more antihypertensive drugs ($p < 0.05$). Nine patients without hypertrophy (25 percent) and 6 patients with hypertrophy (16 percent) were receiving beta adremergic blocking agents; 26 patients in Group I (72 percent) and 17 patients in Group II (46 percent) were receiving diuretic therapy.

Left ventricular size and function: Left ventricular cavity dimensions were normal in all but one patient.

TABLE I

Left Ventricular Anatomy and Function in 73 Hypertensive Patients

	36 Patients With Normal PW Thickness*	37 Patients With LVH*
PW thickness (mm)	9–11 (9.9)†	12–18 (13.4)
IVS thickness (mm)	9–13 (10.5)†	13–18 (14.2)
Patients with DST (n)	3	8
CSA (cm^2)	12.7–26.5 (16.4)†	17.6–41.3 (26.8)
EDD (mm)	37–62 (45)	39–55 (47)
% FS	31–50 (39.5)	26–50 (37.1)

* Mean values in parentheses. † $p < 0.01$.

CSA = cross-sectional area; DST = disproportionate septal thickening; EDD = end-diastolic dimension; IVS = interventricular septum; LVH = left ventricular hypertrophy; % FS = percent fractional shortening; PW = posterior wall.

TABLE II

Clinical Features of 73 Patients With Hypertension

	36 Patients With Normal PW Thickness	37 Patients With LVH
Mean age (yr)	57 ± 12	59 ± 13
Mean BSA (yr)	1.84	1.71
Sex (M/F ratio)	16:20*	26:11
Race (W/B ratio)	34:2	34:3
History of hypertension		
5 yr or less	12	10
Greater than 5 yr	24	27
Blood pressure (mm Hg)		
Range	120–170/70–120	120–240/80–120†
Mean	142/87	154/88
Two or more antihypertensive drugs	32*	22

* $p < 0.05$. † Only one patient had a systolic pressure greater than 180 mm Hg.

B = black; BSA = body surface area; F = female; LVH = left ventricular hypertrophy; M = male; PW = posterior wall; W = white.

The exception was a 47 year old man with a body surface area of 2.2 m^2, a diastolic dimension of 62 mm, percent fractional shortening of 31, septal and posterior wall thicknesses of 10 mm each, blood pressure of 170/120 mm Hg and grade III hypertensive retinopathy; he was on triple drug therapy and had no evidence of left ventricular hypertrophy on electrocardiography. Left ventricular function was normal in all patients in Group I, whereas four patients (11 percent) in Group II with hypertrophy had reduced fractional shortening and diffuse hypokinesia observed on two dimensional echocardiography. There was no left ventricular cavity dilatation in any of the patients with hypertrophy or decreased function.

Electrocardiographic findings: All patients had sinus rhythm except one with atrial fibrillation. Three patients had left anterior fascicular block; all others had a normal frontal plane QRS axis. Nonspecific ST-T wave changes occurred with the same frequency in both patient groups: in 8 (22 percent) of 36 patients in Group I and in 9 (24 percent) of 37 in Group II. With use of the criterion for left ventricular hypertrophy of an R wave in lead aVL of 11 mm or greater, only 4 (11 percent) of the 37 patients in Group II had a positive result, but 2 additional patients in Group I demonstrated left ventricular hypertrophy on electrocardiography. With use of the Sokoloff criteria (S in V_1 + R in V_5 of 35 mm or greater), 7 (19 percent) of 37 patients in Group II

TABLE III

Electrocardiogram in 73 Patients With Hypertension

ECG Criteria of LVH	36 Patients With Normal PW Thickness	37 Patients With LVH
R in aVL ≥ 11 mm	2	4
S in V_1 + R in V_5 ≥ 35 mm	0	7
S in V_1 + R in V_5 + R in aVL	2	9

ECG = electrocardiographic; LVH = left ventricular hypertrophy; PW = posterior wall.

TABLE IV

Evidence of Target Organ Disease in 73 Patients With Hypertension

	36 Patients With Normal PW Thickness	37 Patients With LVH
History of stroke (n)	3	6
Hypertensive retinopathy (grades II or III) (n)	13*	25
Mean serum creatinine (mg/100 ml)	1.09 ± 0.5*	1.58 ± 0.9

* $p < 0.05$.

LVH = left ventricular hypertrophy; PW = posterior wall.

demonstrated electrocardiographic evidence of left ventricular hypertrophy and there were no false positive results in Group I (Table III).

Target organ disease: Although the difference was not statistically significant, six patients with hypertrophy and three patients with normal wall thickness had had a stroke. Patients in Group II with hypertrophy had significantly more hypertensive retinopathy (Table IV); 12 (32 percent) of 37 had grade 0 or I and 25 (68 percent) had grade II or III hypertensive retinopathy. In contrast, 23 (63 percent) of the 36 patients in Group I with normal wall thickness had grade 0 or I retinal findings and only 13 (37 percent) had grade II or III hypertensive retinopathy changes. Impairment of renal function was also more common in Group II; 22 patients (59 percent) in Group II had an elevated serum creatinine level (1.2 mg/100 ml or greater), compared with only 10 patients (28 percent) in Group I ($p < 0.05$) (Table IV).

Discussion

Left Ventricular Hypertrophy

Salcedo et al.[14] reported that two dimensional echocardiography was more accurate than M mode tracings in calculating left ventricular mass in dogs with experimental hypertension. These investigators observed that M mode studies underestimated the thickness of both the ventricular septum and the posterior wall; they also found the two dimensional echocardiogram particularly useful in defining the presence of left ventricular hypertrophy in dogs when there was increased thickness of the anterolateral wall with no significant change in the septal and posterior walls. No clinical studies have been reported in which two dimensional echocardiography has been employed as a quality control check for M mode derivations of left ventricular wall thickness and mass. We not only used two dimensional imaging to monitor the accuracy of the M mode measurements, but we also excluded patients who had segmental wall motion abnormalities without other clinical evidence of previous myocardial infarction. Satisfactory M mode imaging was difficult in several patients in the study group, and without the additional information from two dimensional echocardiography, they would have been excluded. One of the technical problems that contributed to echographic "dropout" of the ventricular sep-

tum with loss of true septal thickness on the recording is attributed to the echographic beam intersecting the septum obliquely because the transducer had to be positioned inferiorly along the left sternal border.

A posterior wall thickness of 12 mm or greater was established as the criterion for left ventricular hypertrophy. We employed the formula used by Sasayama et al.[13] to determine the cross-sectional area of the left ventricle. With use of the cross-sectional area as an index of left ventricular mass, 21 cm^2 was the most appropriate value to separate normal patients from those with increased left ventricular mass (Fig. 3). The three patients who had a mild increase in posterior wall thickness had sufficiently small end-diastolic dimensions that the resultant cross-sectional areas were normal; in contrast, one patient who had a slight increase in cross-sectional area (23 cm^2) with a posterior wall thickness of 11 mm had an end-diastolic dimension at the upper limit of normal. These data reveal that posterior wall thickness is an acceptably good indicator of left ventricular mass as long as the chamber size is normal; however, as the cavity size enlarges, the posterior wall thickness measurement should be expected to underestimate mass.

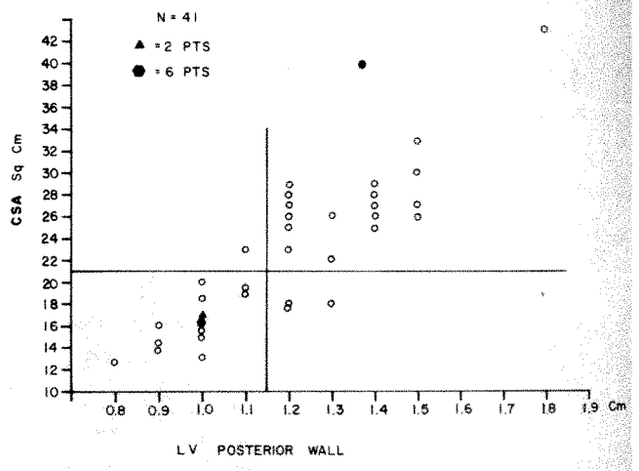

FIGURE 3. The left ventricular (LV) posterior wall thickness is correlated with the cross-sectional area (CSA), which is an index of left ventricular mass. PTS = patients.

Disproportionate Septal Thickening

An association of disproportionate septal thickening (that is, a ventricular septal to left ventricular posterior wall thickness ratio of 1.3 or greater) and hypertension has previously been reported; however, most studies have noted a low incidence rate of 4 to 10 percent.[4,8,10] Our findings were not significantly different: 11 (15 percent) of 73 patients showed disproportionate septal thickening (Table I). Three of the 11 patients had normal thickness of the posterior wall. We found no relation between the presence of disproportionate septal thickening and the duration of the hypertension or the degree of blood pressure elevation. Whether the presence of disproportionate thickening of the septum in hypertensive patients represents an atypical response to the increased afterload or is a coincidental occurrence is not clear. Disproportionate septal hypertrophy has been reported in a much larger proportion (30 to 47 percent) of hypertensive subjects.[15–17] One possible explanation of such a wide range (4 to 47 percent) is measurement error because all determinations were obtained from the M mode scan without the additional benefit of two dimensional imaging. If the M mode echocardiographic beam is directed at a tangent through the septum, the resultant recording may show a falsely thick septum; echo "dropout" (Fig. 2), on the other hand, may cause septal thickness to be underestimated. The combined use of M mode and two dimensional echocardiography should greatly reduce or eliminate the potential for such M mode measurement errors.

Left Ventricular Function

Several years ago Meerson[18] described a pathophysiologic sequence for the development of left ventricular hypertrophy. He reported that the immediate response to a hypertrophy-inducing stimulus imposed on a normally functioning heart was one of physiologic hyperfunction associated with an increase in myocardial protein systhesis. Thus, even before the hypertrophic process causes an increase in left ventricular mass, myocardial function is enhanced in order to overcome its increased pressure work load. This enchancement of left ventricular performance may be observed in patients with aortic stenosis as well as in hypertensive patients.[19]

The end-systolic relations between wall stress and left ventricular diameter did not differ in normal and hypertrophied ventricles.[11] Karliner et al.[6] reported that wall stress in hypertensive patients with left ventricular hypertrophy did not differ significantly from that obtained in normal subjects under basal conditions (167 ± 8.7 compared with 172 ± 6.6 g/cm^2).

Left ventricular ejection phase indexes, including cardiac index, ejection fraction, mean velocity of circumferential fiber shortening and mean normalized systolic ejection rate, were found to be normal in patients with hypertensive hypertrophy.[20] Left ventricular function was impaired only when regional contraction abnormalities or ventricular dilatation, or both, occurred and was inversely related to both cardiac size and systolic wall stress. Strauer[20] concluded that the appropriateness of left ventricular hypertrophy, as a result of mass to volume ratio and stress, is a major determinant of left ventricular performance and of myocardial oxygen consumption. Furthermore, he described two more types of inappropriate left ventricular hypertrophy in patients with hypertensive heart disease: (1) low stress hypertrophy, with an increased mass to volume ratio, normal left ventricular function and normal or reduced myocardial oxygen consumption, and (2) high stress hypertrophy, with normal or low mass to volume ratio, impaired left ventricular function and increased myocardial oxygen consumption. Karliner[6] and Takahashi[12] and their co-workers found no difference in the velocity of circumferential fiber shortening in hypertensive and normal groups. In contrast, however, Frohlich et al.[21] described a reduction in left ventricular

performance in hypertensive patients with left ventricular hypertrophy.

Guazzi et al.[9] *observed a similar functional pattern of the right and left ventricles in hypertensive patients;* this parallel functional pattern of both ventricles suggests a functional interdependence of the two sides that cannot be interpreted in terms of afterload but is probably best explained by changes in the contractile state of the whole heart. Olivari et al.[22] noted that systemic hypertension was associated with mild increases in pulmonary arterial pressure and pulmonary arterial resistance that were not necessarily a consequence of impaired left ventricular function.

Of the 73 hypertensive patients in our study, 4 (5 percent) had decreased left ventricular performance evidenced by fractional shortening of less than 31 percent and mild diffuse hypokinesia on two dimensional studies. None of these patients had left ventricular enlargement. It should be reemphasized that all hypertensive patients with known previous myocardial infarction or segmental wall motion abnormalities on the two dimensional echocardiographic examination were excluded from the study group; therefore the total number of those patients with reduced left ventricular function would be expected to be smaller.

Left Ventricular Wall Thickness: Clinical Correlations

Our findings support the finding of other investigators that echocardiography is the most sensitive clinical method to diagnose left ventricular hypertrophy and measure left ventricular mass. Because of the variability in ventricular septal thickness, the posterior wall is the preferred site to measure.

The small incidence of reduced left ventricular function in our study (4 of 73 patients) could be expected because all but 1 patient had had reasonably good control with therapy and all patients with previous myocardial infarction were excluded. A total of 5 of the original 82 patients referred for the study were excluded because of segmental wall motion abnormalities in the absence of historical or electrocardiographic evidence of previous myocardial infarction. No patient had abnormal left ventricular performance in the absence of left ventricular hypertrophy as determined by cross-sectional area. None of the four patients with reduced function had any enlargement of the left ventricular cavity. These four patients manifested clinical evidence of heart failure; however, no cardiomegaly was demonstrated by roentgenography.

There was a significantly greater proportion of men than of women with left ventricular hypertrophy ($p < 0.05$). Group I (normal subjects) and Group II (patients with hypertrophy) did not differ in age, body surface area or race. Furthermore, in contrast to the report of Ross et al.,[7] the duration of hypertension was not a significant factor in the development of hypertrophy. The mean blood pressure in the two groups did not differ: 142/87 mm Hg in Group I and 154/88 in Group II. A significantly greater number of patients in Group I were receiving two or more antihypertensive drugs ($p < 0.05$). This finding probably reflects better control of blood pressure in patients in Group I who are still without evidence of target organ damage to the heart. This should be a reassuring finding for both the physician and his hypertensive patient. As long as satisfactory control of blood pressure is being achieved, the use of an increasing number of antihypertensive drugs does not correlate with progression of left ventricular hypertrophy.

In light of how much reliability has traditionally been associated with electrocardiography in identifying left ventricular hypertrophy in hypertensive disease, it was disappointing to see how insensitive electrocardiography was in this study. Depending on which electrocardiographic criteria are used, the sensitivity of electrocardiography in diagnosing left ventricular hypertrophy in our patients in Group II ranged from 19 to 24 percent (Table III).

It is not surprising that left ventricular hypertrophy as a manifestation of target organ involvement is associated with a greater incidence of other target organ disease (Table IV). Higher levels of serum creatinine and more severe (grades II and III) hypertensive retinopathy were found in the group with hypertrophy ($p < 0.05$). Although the numbers were too small to have statistical significance, five patients in Group II versus three in Group I had an associated history of stroke.

In summary, combined M mode and two dimensional echocardiography is the most sensitive noninvasive method of measuring left ventricular wall thickness, mass and function. Approximately two thirds of patients with left ventricular hypertrophy will have evidence of significant hypertensive retinopathy or elevated serum creatinine.

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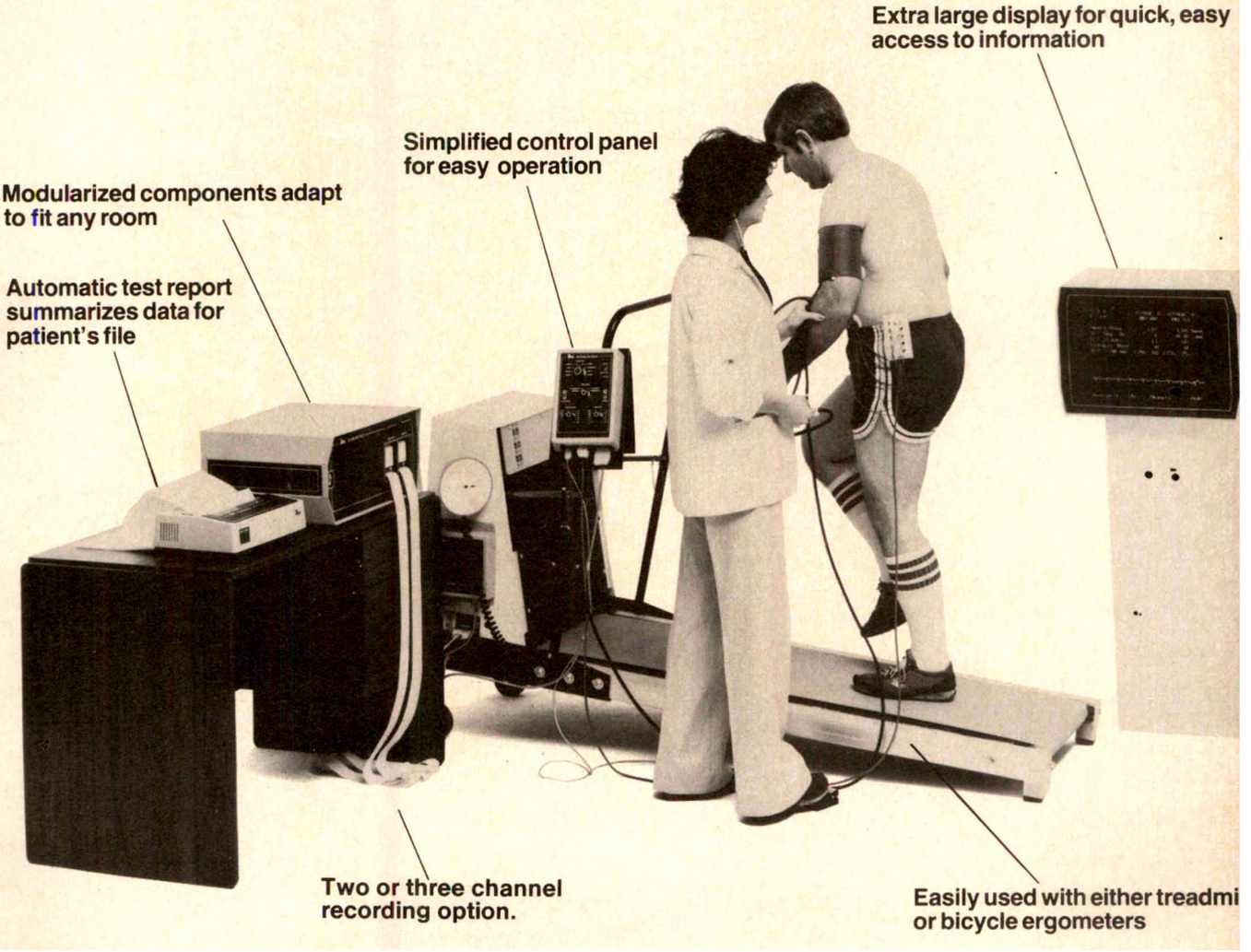

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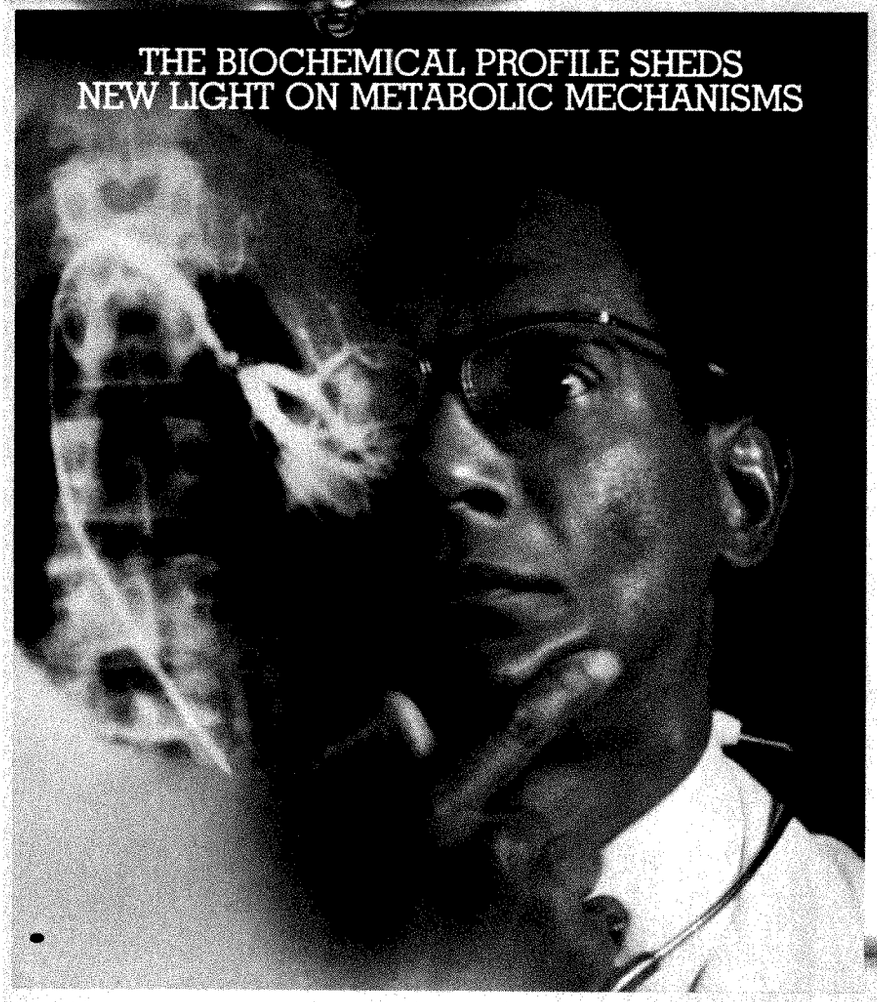


THE BIOCHEMICAL PROFILE SHEDS NEW LIGHT ON METABOLIC MECHANISMS

While hypertension still remains an enigma, its metabolic pathways have become clearer in the past twenty years. One of the most important pathways involves the renin-angiotensin-aldosterone system. The kidney is known to secrete renin under three circumstances: 1) when the organ itself becomes ischemic; 2) when the body's sodium content is depressed; 3) when blood volume is reduced. Renin then catalyzes the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II. Besides being the most potent vasopressor known,[1] angiotensin II also stimulates the adrenal gland to produce aldosterone. By enhancing renal reabsorption of sodium, aldosterone expands the body's sodium content and plasma volume. This reduces renin production and closes the loops of the negative feedback system. A breakdown in this system may result in higher levels of renin and angiotensin II—and sustained high blood pressure.

Disturbances in other mechanisms can also trigger metabolic chains of events that lead to hypertension. This increasing knowledge has generated interest in drugs designed to halt the hypertensive process at several points. One of the newest drugs is thought to inhibit the enzyme that converts angiotensin I into angiotensin II.[1] Equally important has been the development of more accurate diagnostic tests for "biochemical" profiling.

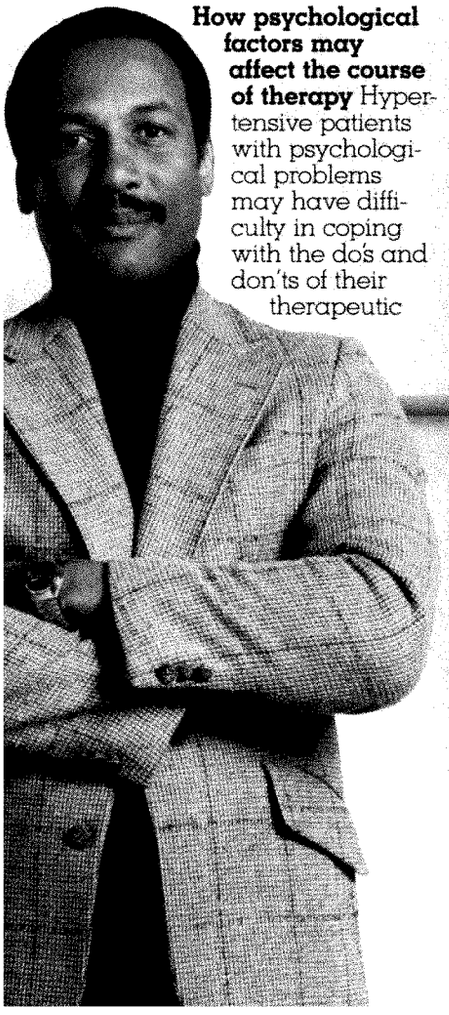
How useful is measuring renin activity? Some clinicians now advocate "renin profiling" of all hypertensives. This rather complicated test provides the renin-sodium index by indirectly measuring the renin level and comparing it to sodium intake. The index helps distinguish renin-dependent hypertensives (about 70% of patients) from those who are sodium-dependent. It is only the latter who are most likely to benefit from diuretics and the "stepped-care" approach.

While renin profiling can be very useful for selected patients, most physicians consider it unnecessary or impractical for routine evaluation. The initial choice of therapy rarely hinges on renin activity.[2] Also, the renin-sodium index is hard to obtain in non-hospitalized patients and may not offer any real advantages over a therapeutic trial that includes a diuretic (for low-renin patients) or a beta blocker (for high-renin patients).[2,3]

The lab workup that works for most patients Some authorities believe that a minimal workup is sufficient for roughly 90% of hypertensive patients.[3] This generally includes a hematologic profile, urinalysis, blood chemistry (covering a number of biochemical variables), along with the standard ECG and chest roentgenogram.[2,3] More exhaustive tests—including renal profiling, intravenous urograms and catecholamine level determinations—would only be ordered if secondary causes are suspected.

THE "PSYCHOLOGICAL PROFILE" ADDS VALUABLE INSIGHTS

At times, it reveals excessive anxiety A good deal of research has focused on the contributory role of psychological and social factors in the development of hypertension. Such factors have been found to increase plasma renin activity.[4] Consequently it is often recommended that some form of psychosocial profile be added to the patient's family and medical history.[2,5] Even though the hypertensive patient may seem calm, a few carefully worded questions often uncover intense psychic tension. The patient's anxiety may center on his psychological problems alone or may extend to the economic and social repercussions of his illness.



How psychological factors may affect the course of therapy Hypertensive patients with psychological problems may have difficulty in coping with the do's and don'ts of their therapeutic program . . . and with demoralizing new self-images as "chronically sick, potentially dependent" persons. The psychological profile helps the physician assess the patient's understanding of his illness, his emotional reactions to it, and the likelihood of his compliance with recommended therapy. This information can help set the stage for the mutually rewarding doctor-patient rapport essential to successful long-term management of any chronic illness.

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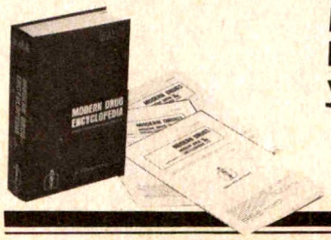

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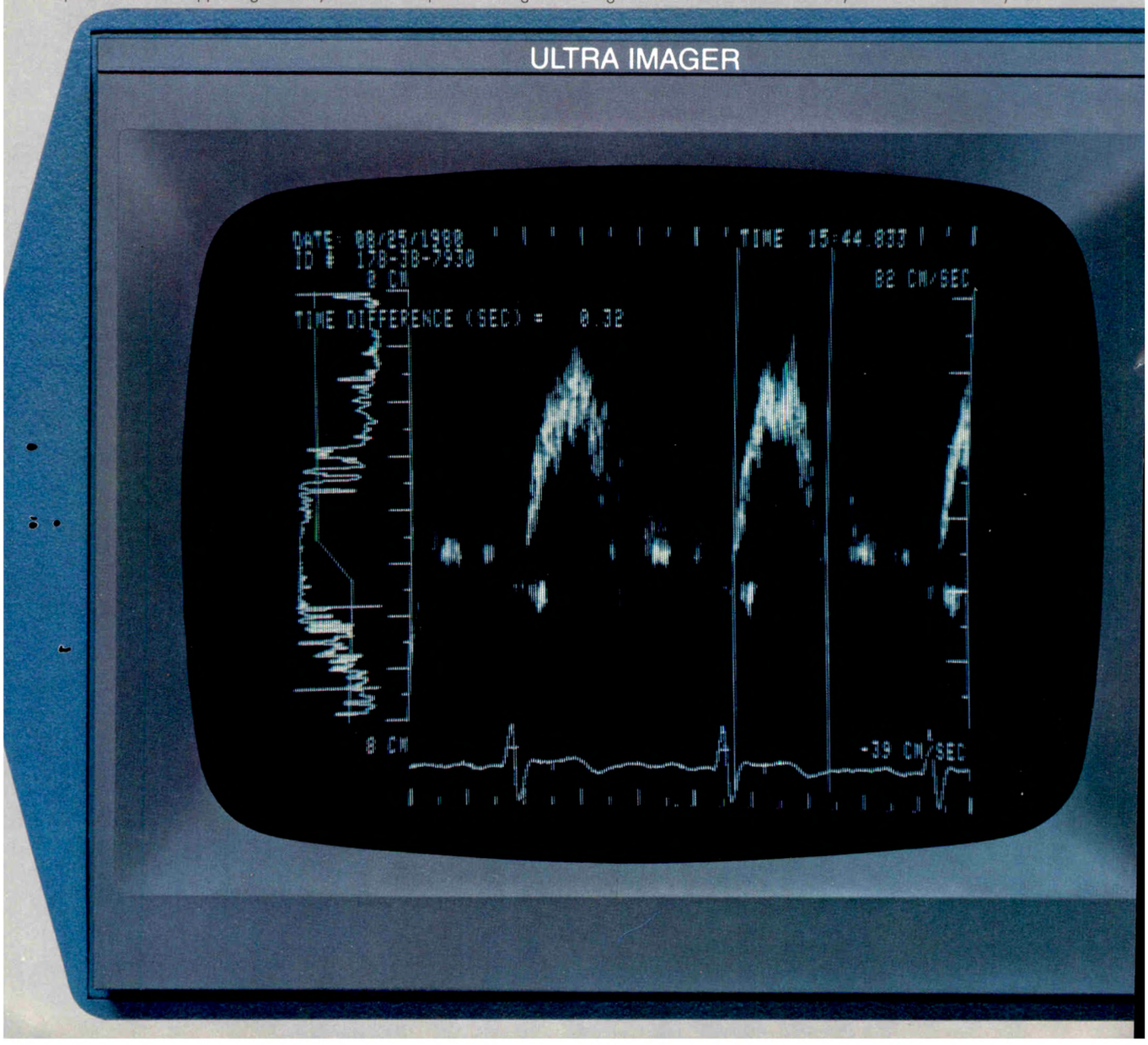

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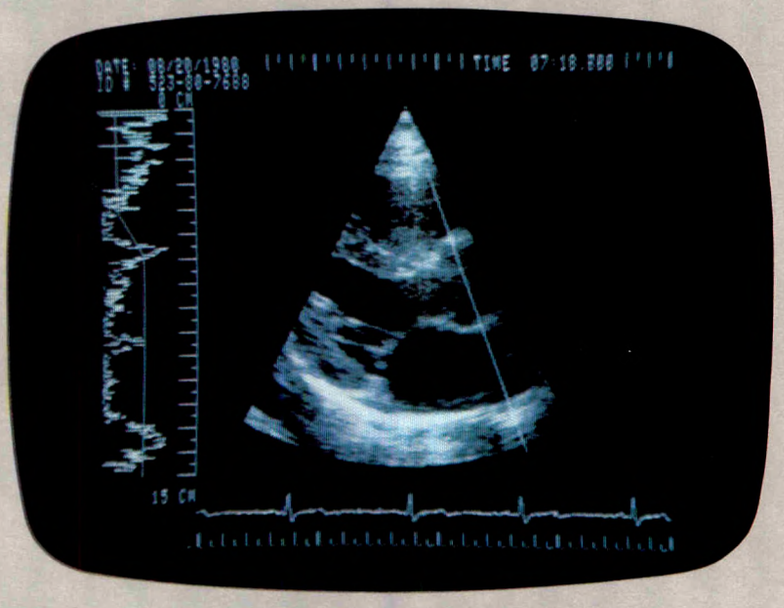

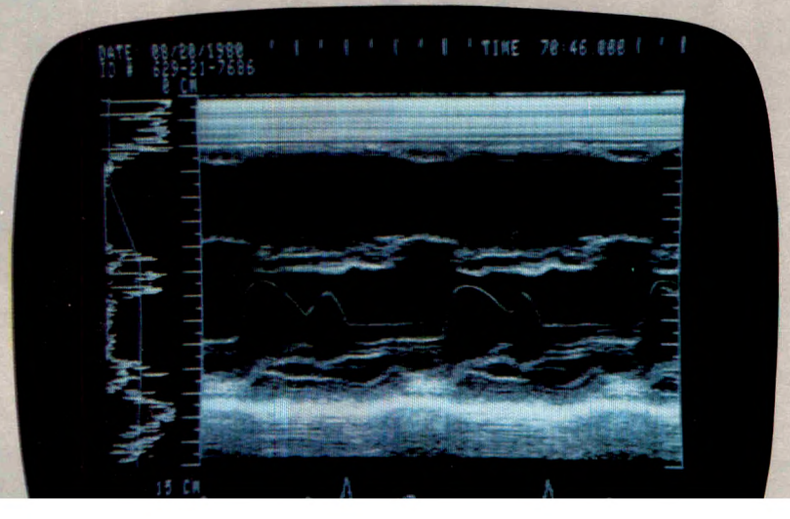

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The Ultra Imager also provides diagnostic quality physiological signal conditioning. Every system includes an ECG channel and can accommodate optional pulse/phono and respiration channels.

Cost-effectiveness built into the Ultra Imager System

The Ultra Imager offers many cost-effective features that enhance its value to cardiology practice. The mechanical sector scan was selected for the system because it offers superior performance in 2D/Doppler imaging at lower cost. In addition, it will permit ready adaptation to future transducer technologies.

Ease of maintenance is again achieved, along with greater electronic stability, by comprehensive digital processing throughout the system. Integrated design of the Ultra Imager avoids the cabling connections and duplicated components associated with the "stacked box" approach.

The system's digital scan converter (image memory) provides you with non-fade displays and gives you instantaneous freeze-frames in any mode without flickering or fading. These advanced display capabilities facilitate diagnostic review and the measurement and recording of scan data.

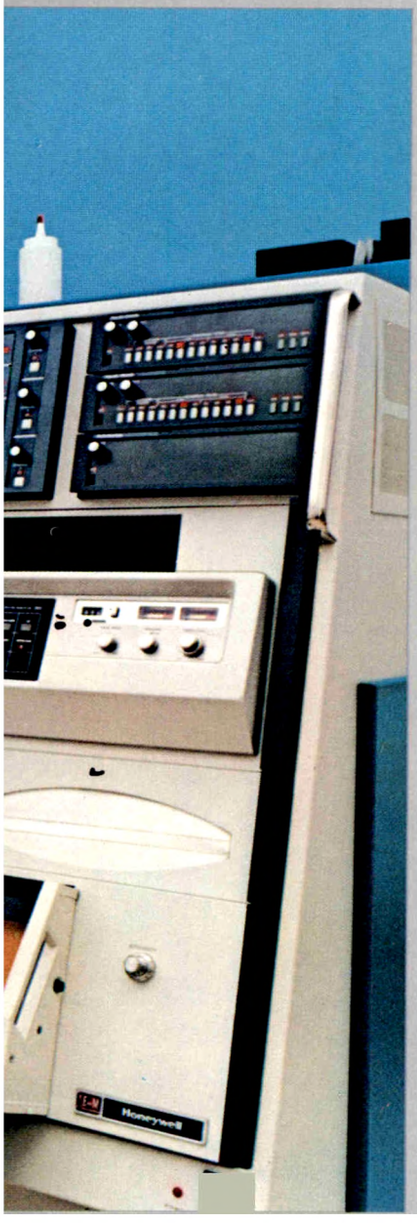
The unique Auto-Test feature of the Ultra Imager allows the system to test itself for failures. If a failure exists, an appropriate indicator light signals the source of the failure. This simplifies servicing of the instrument.

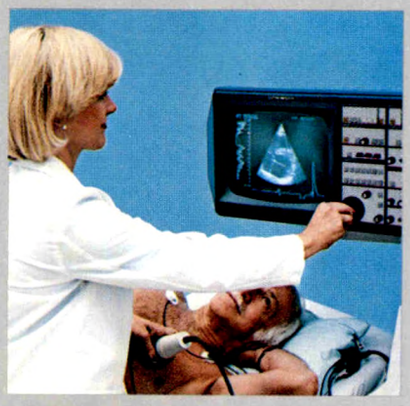
Human engineered with unique operator convenience features

Through careful attention to human engineering details, we have made a sophisticated imaging system easy to operate. For instance, both the monitor and primary control panel are on a movable gantry that can be positioned near the patient for ease of use and viewing. This makes system controls conveniently accessible to the operator while at the patient's bedside.

The Ultra Imager also includes an audiovisual self-teaching feature which employs the system's videotape recorder to play training programs produced by E for M/Honeywell. This convenient feature makes staff training a much simpler procedure.

For operator convenience, all displays can be viewed easily even in a daylit room. There is also built-in storage space for gels, tissues, paper and other supplies. Because the cart is compact and easily maneuvered, it can be moved wherever needed.





Operator can position the transducer and be within convenient reach of all necessary scan controls.

Cardiologist can perform off-line data analysis while listening to voice annotations recorded by the operator.

Audiovisual self-teaching feature facilitates training of new personnel.

A versatile imaging system that offers more diagnostic information and greater clinical utility.

Today the key to diagnostic value in an echocardiography system is the availability of accurate and repeatable pulsed Doppler images. The Ultra Imager offers you this plus the complementary imaging capabilities you need to perform cardiac examinations.

Using a sophisticated spectral analysis technique called Fast Fourier Transform (FFT) the Ultra Imager can process Doppler blood velocity data in real time without the need for an operator to calibrate gain and threshold settings. This makes quantitation of blood flow patterns and flow rates throughout the heart a much simpler clinical procedure.

The Ultra Imager's built-in versatility is made possible by a unique, dedicated array processor designed to handle the high-speed computations required for repeatable Doppler imaging. The computing power of this separate processor makes it possible to combine accurate blood velocities with 2D imaging data to provide the essential measurements for determining stroke volume and cardiac output. The Ultra Imager is the only 2D/Doppler System available offering this level of diagnostic versatility.

Honeywell's new LS-8 recorder is a standard system feature. It allows you to make a hard copy of the display with full gray scale reproduction and high resolution. You can select page print or strip chart modes and get crisp, black-on-white records with immediate dry processing.

High quality videotaped images are formatted to allow off-line data analysis on playback images. This storage feature allows both physician and operator to conduct diagnostic reviews when it is most convenient.

The E for M/Honeywell Commitment

E for M/Honeywell has a special commitment to cardiology. Because we've worked with you for over 30 years, we know the kind of service and performance you demand from a medical instrument company. Over the years, we've developed a professional rapport which has led to the development and manufacture of many of the best-engineered, high performance instruments in the healthcare field. The Ultra Imager is one more example of this continuing commitment to excellence.

Service

The Ultra Imager is supported in the field by our own specially trained ultrasound service technicians. Because there are over 40 service locations in the U.S. alone, E for M/Honeywell service is fast and responsive. A toll-free number connected to the Ultra Imager Support Center makes service available 24 hours a day.

The Ultra Imager's Auto-Test feature further minimizes downtime by pinpointing any failures in the system. Now if a service call is needed the technician knows which parts are required to repair the system on-site. In addition, the Repair/Exchange program provides immediate replacement parts for your service technician with the lowest possible board repair cost through the use of Automatic Test Equipment at the factory.

Quality Assurance

The Ultra Imager was designed with reliability and ease of maintenance in mind. "MIL-Spec" reliability analyses were used to evaluate every aspect of the system design. Each subassembly has been thoroughly tested individually and as part of the complete system. And every completed unit is subjected to rigorous temperature cycling so that any marginal components can be replaced in the factory. This means that the system we install for you is in optimum working order.

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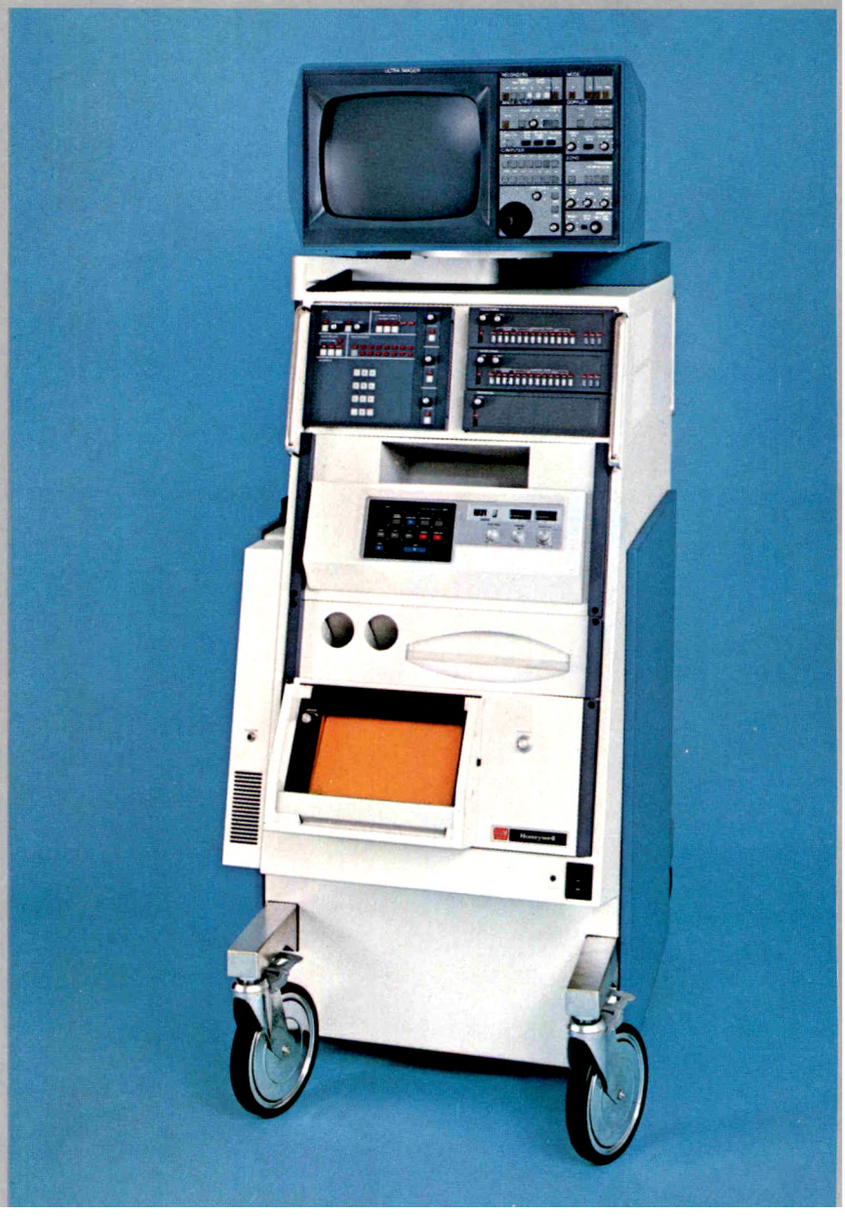

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Clinicopathologic Correlates of Acute Ischemic Heart Disease Syndromes

L. MAXIMILIAN BUJA, MD, FACC
JAMES T. WILLERSON, MD, FACC

Dallas, Texas

To better define the relations among acute and chronic coronary arterial lesions and different syndromes of acute ischemic heart disease, the clinicopathologic findings in 100 recent myocardial infarcts in 83 patients were reviewed and the results correlated with those of previous studies. Severe atherosclerosis (greater than 75 percent narrowing of luminal cross-sectional area) involved three or more major coronary arteries in 65 percent; two arteries in 16 percent, one artery in 15 percent, and no arteries in 4 percent of cases. The incidence rate of recent occlusive coronary arterial lesions was 61 percent, including 50 (90.2 percent) of 55 grossly apparent transmural infarcts, 9 (34.6 percent) of 26 grossly evident subendocardial infarcts and 2 (10.5 percent) of 19 multifocal microinfarcts associated with clinical episodes of acute coronary insufficiency ($p < 0.001$). The 61 recent occlusive lesions consisted of two thromboemboli, two isolated plaque hemorrhages and 57 in situ thrombi that were associated with a high incidence rate of plaque erosion, rupture and hemorrhage. Clinical conditions predisposing to reduced coronary perfusion were identified before the onset of 26.2 percent of infarcts with recent occlusions and 61.5 percent of infarcts without recent occlusions ($p < 0.001$). Clinical onset of infarction was followed by severe cardiac pump failure or congestive heart failure in 63.9 percent of infarcts with and 41.0 percent of infarcts without recent occlusions ($p = 0.04$).

From this and previous studies, it is concluded that (1) acute ischemic heart disease does not have a constant relation with the severity of chronic atherosclerosis; (2) myocardial necrosis commonly occurs in the absence of acute permanent coronary occlusion, but in this setting is usually limited to subendocardial involvement of variable extent; (3) acute coronary thrombosis frequently acts as a major factor in determining the extent and distribution of an evolving infarct, as indicated by the large incidence of occlusive coronary thrombi with regional transmural infarcts; and (4) coronary thrombus formation is not dependent on a generalized impairment of coronary perfusion, either before or after the onset of infarction.

From the Departments of Pathology and Internal Medicine (Cardiac Unit), Southwestern Medical School, The University of Texas Health Science Center at Dallas, Dallas, Texas. This study was supported in part by Ischemic Heart Disease (SCOR) Grant HL-17669 from the National Institutes of Health, Bethesda, Maryland. Manuscript received June 30, 1980; revised manuscript received September 2, 1980, accepted September 9, 1980.

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Numerous clinicopathologic studies of patients with fatal ischemic heart disease have previously been reported in an attempt to define the pathogenesis of the clinical syndromes.[1–29] However, controversy remains regarding the frequency and significance of severe atherosclerosis, acute coronary thrombi and other acute coronary lesions in patients with acute myocardial infarction and other ischemic heart disease syndromes. A new dimension to this issue has been added with evidence that coronary arterial spasm may act as a pathophysiologic factor in patients with typical and atypical angina pectoris and acute myocardial infarction.[29–36] This study was undertaken to document pertinent findings in a group of hospitalized patients with autopsy evidence of ischemic heart disease

and recent myocardial necrosis, including patients with a clinical diagnosis of acute myocardial infarction and patients with unstable angina pectoris or other forms of acute coronary insufficiency.[37]

Two important features of the study were that (1) all myocardial infarcts occurring within 3 months of death were included whether or not death directly resulted from the infarct, and (2) each pathologic lesion was correlated with clinical findings occurring before and after the clinical onset of infarction. The study was limited to myocardial lesions occurring within 3 months of death because morphologic methods can be used to estimate the age of myocardial and coronary lesions occurring within this time interval on the basis of recognition of stages in the organization and healing process.[15,25,38–40] The goals of this study were: (1) to define more clearly the roles of coronary atherosclerosis and acute coronary lesions, including thrombosis, in the development of clinical coronary insufficiency and acute myocardial infarction; (2) to correlate the findings with those of previous clinicopathologic studies; and (3) to obtain thereby a broader perspective concerning the clinicopathologic features of acute ischemic heart disease.

Methods

Patients studied: The study group was derived from patients who came to autopsy over a 5 1/2 year period (1974 to 1979) at Parkland Memorial Hospital or the Veterans Administration Hospital in Dallas, Texas. The study was limited to 83 patients whose heart was examined for research purposes in a detailed and systematic fashion at the time of autopsy. The autopsy and clinical findings were subsequently reviewed when the data presented herein were compiled.

Two groups of patients were included in the study: (1) 71 patients with autopsy evidence of one or more discrete, usually grossly obvious, recent myocardial infarcts, with or without a definite clinical diagnosis of myocardial infarction, and (2) 19 patients, including 7 from the first group, with autopsy evidence of recent multifocal myocardial necrosis, confirmed histologically, and a clinical history compatible with some type of acute coronary insufficiency syndrome including unstable angina pectoris or recurrent severe angina pectoris. Patients in the category of sudden death without demonstrable myocardial necrosis were not included in this study because of the nature of the patient group and the criteria for inclusion in the study.

An event (myocardial infarction or coronary insufficiency) was defined as recent if autopsy and clinical evidence indicated an occurrence within 3 months of death. The study was limited to myocardial infarcts that developed spontaneously and did not include myocardial infarcts that developed as a possible sequela of cardiac surgery or other diagnostic or therapeutic procedures.

A clinical diagnosis of acute myocardial infarction was based on standard criteria including a history of prolonged chest pain, a clearly abnormal evolutionary pattern of serum enzyme tests including increased serum creatine kinase (CK) and, more recently, increased CK-MB or CK-B isoenzymes, as well as diagnostic or compatible electrocardiographic changes or a positive technetium-99m stannous pyrophosphate myocardial scintigram, or both. A clinical diagnosis of acute coronary insufficiency was made when clinical symptoms were suggestive of episodes of prolonged myocardial ischemia but a definitive diagnosis of acute myocardial infarction was not made. Most patients in the group with acute coronary insufficiency had the diagnosis of unstable angina pectoris, which was defined as severe, recurrent and progressive chest pain that was of recent onset or represented a change in pattern in a patient with previously stable angina.[37] Other acute coronary insufficiency syndromes were diagnosed clinically as recurrent severe angina pectoris and recurrent acute pulmonary edema.

Autopsy studies: The hearts were initially examined in the fresh state but, in some cases, after fixation in a phosphate-buffered solution of 10 percent formalin. Postmortem coronary angiographic procedures were rarely performed. The major coronary arteries were dissected by making multiple transverse cuts at 3 to 5 mm intervals. If the coronary arteries were heavily calcified, fixation and decalcification were performed before extensive coronary dissection was undertaken. This was accomplished either by removal of major coronary segments from the hearts before processing or by incubation of the entire heart in a decalcification solution before the coronary arteries were sectioned in situ.

After gross examination of the coronary arteries, coronary lesions were marked on a standard diagram. For each coronary artery (left main, left anterior descending, left diagonal or marginal (or both), left circumflex and right coronary artery), the extent and severity of coronary artery disease was noted. An estimate was made of the percent narrowing of the luminal cross-sectional area produced by the lesion, taking into account postmortem collapse of the vessels. Selected areas of the coronary arteries were processed for histologic examination, including all occlusive lesions, lesions representing sites of maximal luminal narrowing for all coronary arteries, and representing areas distal to sites of maximal narrowing. Blocks containing occlusive lesions were frequently step-sectioned, but serial sectioning was not performed. Histologic examination was used to evaluate the nature of the coronary arterial lesions as well as to confirm the gross impression regarding percent luminal narrowing.

The heart was opened in most cases by cutting the ventricles into several transverse slices ("breadloafing technique"). Heart weight was determined and evidence of chamber hypertrophy and dilatation and focal lesions were noted. The location and relative size of all grossly visible myocardial infarcts were recorded. Histologic sections of myocardium were prepared and examined in each case. The age of each myocardial infarct was estimated using standard gross and histologic criteria.[25,26,38–40] An infarct was designated transmural if the infarct exhibited prominent involvement of the outer as well as the inner half of the left ventricular wall and subendocardial if it was essentially confined to the inner half of the left ventricular wall. In addition to discrete myocardial infarcts, evidence was recorded of multifocal small foci of myocardial necrosis or fibrosis. These lesions were often detectable only microscopically, but were occasionally extensive enough to be grossly visible. Recent multifocal microinfarcts in the patients with evidence of acute coronary insufficiency consisted of foci of acute or organizing necrosis or myocytolysis, or both.[25,26,38–40]

Statistical analysis: Standard chi-square analysis was used to test for differences in the incidence of coronary arterial lesions between different types of myocardial infarcts (Table I) and between infarcts of different ages (Table II). Chi-square analysis was also used to test for differences in the incidence of various autopsy and clinical findings between infarcts with

TABLE I

Recent Coronary Arterial Lesions in Patients With Recent Myocardial Infarcts

	Gross Transmural Infarcts	Gross Subendocardial Infarcts	Multifocal Microinfarcts	All Infarcts
Cases (n)	55	26	19	100
No recent coronary lesion	3 (5.5%)	16 (61.5%)	16 (84.2%)	35 (35%)
Nonocclusive mural thrombus	2 (3.6%)	1 (3.8%)	1 (5.3%)	4 (4%)
Occlusive plaque hemorrhage	1 (1.8%)	1 (3.8%)	0 (0%)	2 (2%)
Occlusive thromboembolus	2 (3.6%)	0 (0%)	0 (0%)	2 (2%)
Occlusive in situ thrombus	47 (85.5%)	8 (30.8%)	2 (10.5%)	57 (57%)
Any recent occlusive lesion	50 (90.2%)	9 (34.6%)	2 (10.5%)	61 (61%)
Severe atherosclerosis (>75% narrowing of luminal area) in artery with recent lesion				
Any level	47/52 (90.4%)	7/10 (70.0%)	3/3 (100%)	57/65 (87.7%)
Lesion site	44/52 (84.6%)	6/10 (60.0%)	3/3 (100%)	53/65 (81.5%)
Distal artery	32/52 (61.5%)	6/10 (60.0%)	3/3 (100%)	41/65 (63.1%)

n = number.

and without associated acute coronary occlusive lesions (Tables III to V).

Results

Autopsy Findings

Myocardial infarcts: At autopsy, 81 discrete, usually grossly obvious, recent myocardial infarcts and 19 multifocal microinfarcts were identified (Tables I to III). Of the 100 myocardial infarcts, 67 had clinicopathologic features consistent with an age of 12 hours to 20 days and 33 had features consistent with an age of 3 weeks to 3 months. Each of the 81 gross myocardial infarcts had a discrete focus of coagulation necrosis or of granulation and fibrous tissue consistent with previous coagulation necrosis. Of the 81 gross myocardial infarcts, 55 were transmural and 26 were subendocardial. Of the 55 transmural infarcts, 27 were anterior, 23 inferoposterior, and 5 both anterior and posterior. Of the 26 subendocardial infarcts, 8 were anterior and 10 inferoposterior; 8 exhibited anterior as well as posterior or circumferential involvement. On histologic examination, the 19 multifocal microinfarcts were predominantly located in the subendocardium and consisted of variable combinations of coagulation necrosis, myocytolysis, granulation tissue and fibrosis (Fig. 1).

Associated coronary arterial lesions: The myocardial infarcts were associated with coronary atherosclerosis of variable extent and severity and occurred with and without demonstrable recent coronary arterial lesions. Of the 100 myocardial infarcts, 61 were associated with recent coronary occlusive lesions, 4 were associated with small nonocclusive mural thrombi and 35

TABLE II

Coronary Arterial Lesions With Recent Myocardial Infarcts of Different Ages

	Infarct Age of 12 Hours to 20 Days	Infarct Age of 3 Weeks to 3 Months	All Infarcts
Cases (n)	67	33	100
Any recent occlusive lesion	41 (61.2%)	20 (60.6%)	61 (61%)
Occlusive in situ thrombosis	37 (55.2%)	20 (60.6%)	57 (57%)
Thrombus only	12/37 (32.4%)	16/20 (80.0%)	28/57 (49.1%)
Thrombus and plaque hemorrhage	9/37 (24.3%)	0/20 (0%)	9/57 (15.8%)
Thrombus with plaque hemorrhage and plaque rupture or erosion	16/37 (43.3%)	4/20 (20.0%)	20/57 (35.1%)

TABLE III

Autopsy Findings in Hearts of Patients With Recent Myocardial Infarcts

	Gross Transmural Infarcts		Gross Subendocardial Infarcts		Multifocal Microinfarcts		All Infarcts		
	Occl	No Occl	Occl	No Occl	Occl	No Occl	Occl	No Occl	Total
Number of infarcts with and without associated recent coronary occlusions	50	5	9	17	2	17	61	39	100
Heart weight over 400 g	43 (86.0%)	5 (100%)	9 (100%)	15 (88.2%)	1 (50%)	12 (70.6%)	53 (86.9%)	32 (82.1%)	85 (85.0%)
Number of coronary arteries with severe atherosclerosis (>75% narrowing of luminal area)									
0	1 (2.0%)	1 (20.0%)	1 (11.1%)	1 (5.8%)	0 (0%)	0 (0%)	2 (3.3%)	2 (5.1%)	4 (4.0%)
1	10 (20.0%)	1 (20.0%)	0 (0%)	2 (11.8%)	0 (0%)	2 (11.8%)	10 (16.4%)	5 (12.8%)	15 (15.0%)
2	11 (22.0%)	1 (20.0%)	0 (0%)	2 (11.8%)	0 (0%)	2 (11.8%)	11 (18.0%)	5 (12.8%)	16 (16.0%)
3–5	28 (56.0%)	2 (40.0%)	8 (88.9%)	12 (70.6%)	2 (100%)	13 (76.4%)	38 (62.3%)	27 (69.3%)	65 (65.0%)
Previous discrete myocardial infarct(s) or patchy fibrosis, or both	30 (60.0%)	5 (100%)	6 (66.7%)	16 (94.1%)	1 (50%)	12 (70.6%)	37 (60.7%)	33 (84.6%)	70 (70.0%)
Recent myocardial infarct									
Anterior	23 (46.0%)	4 (80.0%)	2 (22.2%)	6 (35.3%)	0 (0%)	0 (0%)	25 (41.0%)	10 (25.6%)	35 (35.0%)
Inferoposterior	23 (46.0%)	0 (0%)	4 (44.4%)	6 (35.3%)	0 (0%)	0 (0%)	27 (44.3%)	6 (15.4%)	33 (33.0%)
Anterior and posterior or circumferential	4 (8.0%)	1 (20.0%)	3 (33.3%)	5 (29.4%)	0 (0%)	0 (0%)	7 (11.5%)	6 (15.4%)	13 (13.0%)
Multifocal microinfarcts	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (100%)	17 (100%)	2 (3.3%)	17 (43.6%)	19 (19.0%)

Occl = recent coronary arterial occlusion.

TABLE IV

Clinical Cardiovascular Alterations Before Clinical Onset of Myocardial Infarction

	Gross Transmural Infarcts		Gross Subendocardial Infarcts		Multifocal Microinfarcts		All Infarcts		
	Occl	No Occl	Occl	No Occl	Occl	No Occl	Occl	No Occl	Total
Cases (n)	50	5	9	17	2	17	61	39	100
Angina pectoris	33 (66.0%)	3 (60.0%)	6 (66.7%)	8 (47.1%)	2 (100%)	16 (94.1%)	41 (67.2%)	27 (69.2%)	68 (68.0%)
Hypertension	24 (48.0%)	3 (60.0%)	7 (77.8%)	4 (23.5%)	1 (50.0%)	9 (52.9%)	32 (52.5%)	16 (41.0%)	48 (48.0%)
Alterations predisposing to reduced coronary perfusion									
Congestive heart failure	14 (28.0%)	3 (60.0%)	2 (22.2%)	5 (29.4%)	0 (0%)	7 (41.2%)	16 (26.2%)	15 (38.5%)	31 (31.0%)
Aortic stenosis	0 (0%)	0 (0%)	0 (0%)	5 (29.4%)	0 (0%)	1 (5.9%)	0 (0%)	6 (15.4%)	6 (6.0%)
Shock (septic, toxic)	0 (0%)	0 (0%)	0 (0%)	3 (17.6%)	0 (0%)	0 (0%)	0 (0%)	3 (7.6%)	3 (3.0%)
None	36 (72.0%)	2 (40.0%)	7 (77.8%)	4 (23.6%)	2 (100%)	9 (52.9%)	45 (73.8%)	15 (38.5%)	60 (60.0%)

Occl = recent coronary arterial occlusion.

TABLE V

Clinical Course After Clinical Onset of Myocardial Infarction

	Gross Transmural Infarcts		Gross Subendocardial Infarcts		Multifocal Microinfarcts		All Infarcts		
	Occl	No Occl	Occl	No Occl	Occl	No Occl	Occl	No Occl	Total
Cases (n)	50	5	9	17	2	17	61	39	100
Early onset, fatal cardial pump failure*	28 (56.0%)	2 (40.0%)	0 (0%)	10 (58.8%)	1 (50.0%)	0 (0%)	29 (47.5%)	12 (30.8%)	41 (41.0%)
Late onset, fatal cardiac pump failure	2 (4.0%)	0 (0%)	1 (11.1%)	0 (0%)	0 (0%)	0 (0%)	3 (4.9%)	0 (0%)	3 (3.0%)
Fatal chronic CHF	5 (10.0%)	1 (20.0%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	5 (8.2%)	2 (5.1%)	7 (7.0%)
Chronic CHF, cardiac operation,† early postoperative death	2 (4.0%)	0 (0%)	0 (0%)	1 (5.9%)	0 (0%)	1 (5.9%)	2 (3.3%)	2 (5.1%)	4 (4.0%)
Fatal cardiac arrhythmia	7 (14.0%)	1 (20.0%)	1 (11.8%)	2 (11.1%)	0 (0%)	4 (23.5%)	8 (13.1%)	7 (17.9%)	15 (15.0%)
Survived without pump failure or CHF; subsequently had:									
Fatal new myocardial infarct	1 (2.0%)	0 (0%)	5 (55.6%)	3 (17.6%)	0 (0%)	3 (17.6%)	6 (9.8%)	6 (15.4%)	12 (12.0%)
Unstable angina pectoris, CABG, early postoperative death‡	3 (6.0%)	1 (20.0%)	2 (22.2%)	0 (0%)	1 (50.0%)	9 (52.9%)	6 (9.8%)	10 (25.6%)	16 (16.0%)
Death from metastatic cancer	2 (4.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (3.3%)	0 (0%)	2 (2.0%)

* One patient died after coronary arterial bypass surgery performed after the clinical onset of infarction and pump failure. † Cardiac operations consisted of ventricular aneurysm resections in 2 cases, coronary arterial bypass surgery in 1 and aortic valve replacement in 1 case. ‡ Death resulted from cardiac pump failure or arrhythmias, or both, and occurred within 1 to 2 days of operation in 15 cases and after 10 days in 1 case.
CABG = coronary arterial bypass graft; CHF = congestive heart failure; Occl = recent coronary arterial occlusion.

occurred without a demonstrable recent coronary lesion (Table I). The occlusive nature of the lesions was originally evaluated on gross examination. On subsequent light microscopic examination, the occlusive lesions generally showed 100 percent stenosis, although some were associated with very small lumens, which could be accounted for by real or artifactual retraction of thrombus or by recanalization of older thrombi. The 61 occlusive lesions consisted of 2 thromboemboli (defined by previously described criteria),[10] 2 plaque hemorrhages and 57 in situ thrombi (Fig. 2 to 4). Two of the recent occlusive thrombi occurred in atheromatous saphenous vein bypass grafts implanted, respectively, 4 and 6 years previously; the other occlusive lesions occurred in the native coronary arterial circulation.

Recent coronary occlusive lesions: Recent coronary occlusive lesions were associated with 90.2 percent of gross transmural infarcts, 34.6 percent of gross subendocardial infarcts and 10.5 percent of multifocal microinfarcts ($p < 0.001$) (Table I). The interval between occurrence of infarction and death did not have an influence on the detection of coronary occlusive lesions (Table II). Coronary occlusions were detected in association with 61.2 percent of infarcts 12 hours to 20 days old and 60.6 percent of infarcts 3 weeks to 3 months old. The recent myocardial and coronary lesions exhibited generally similar histologic ages, but no attempt was made to determine precisely the relative ages of infarcts and coronary lesions using histologic criteria. The age of the infarct did influence the detection of lesions associated with coronary thrombi because 67.6 percent of coronary thrombi associated with prominent plaque hemorrhage as well as erosion or rupture, or both, occurred with infarcts 12 hours to 20 days old; whereas only 20 percent of thrombi associated with such changes occurred with infarcts 3 weeks to 3 months old ($p = 0.002$). The overall incidence rate of plaque lesions with thrombi was 50.9 percent. Plaque erosion was identified as thinning, degeneration and loss of structural integrity of the fibrous capsule of an atheromatous plaque (Fig 2 and 3), and plaque rupture as a prominent complete break and separation of the capsule (Fig. 4). Plaque disruption was associated with prominent intraplaque hemorrhage and, in some cases, with atheromatous material (foam cells and cholesterol clefts) in the overlying thrombus or lumen of the distal vessel (Fig. 4).

Each of the recent coronary lesions was associated with a single myocardial infarct and, conversely, only one recent coronary lesion was associated with a given infarct. Of the 65 recent occlusive and nonocclusive lesions, 12.3 percent occurred in vessels with minimal to moderate old atherosclerosis and 87.7 percent in vessels with at least focally severe atherosclerosis (Table I). Atherosclerotic narrowing was severe (greater than 75 percent reduction in luminal area) at the site of the recent lesion in 81.5 percent of cases, but severe narrowing of the artery distal to the recent lesion occurred in only 63.1 percent. The recent coronary lesions were generally located in the vessels that supplied the infarcted region. In the seven cases of recent coronary

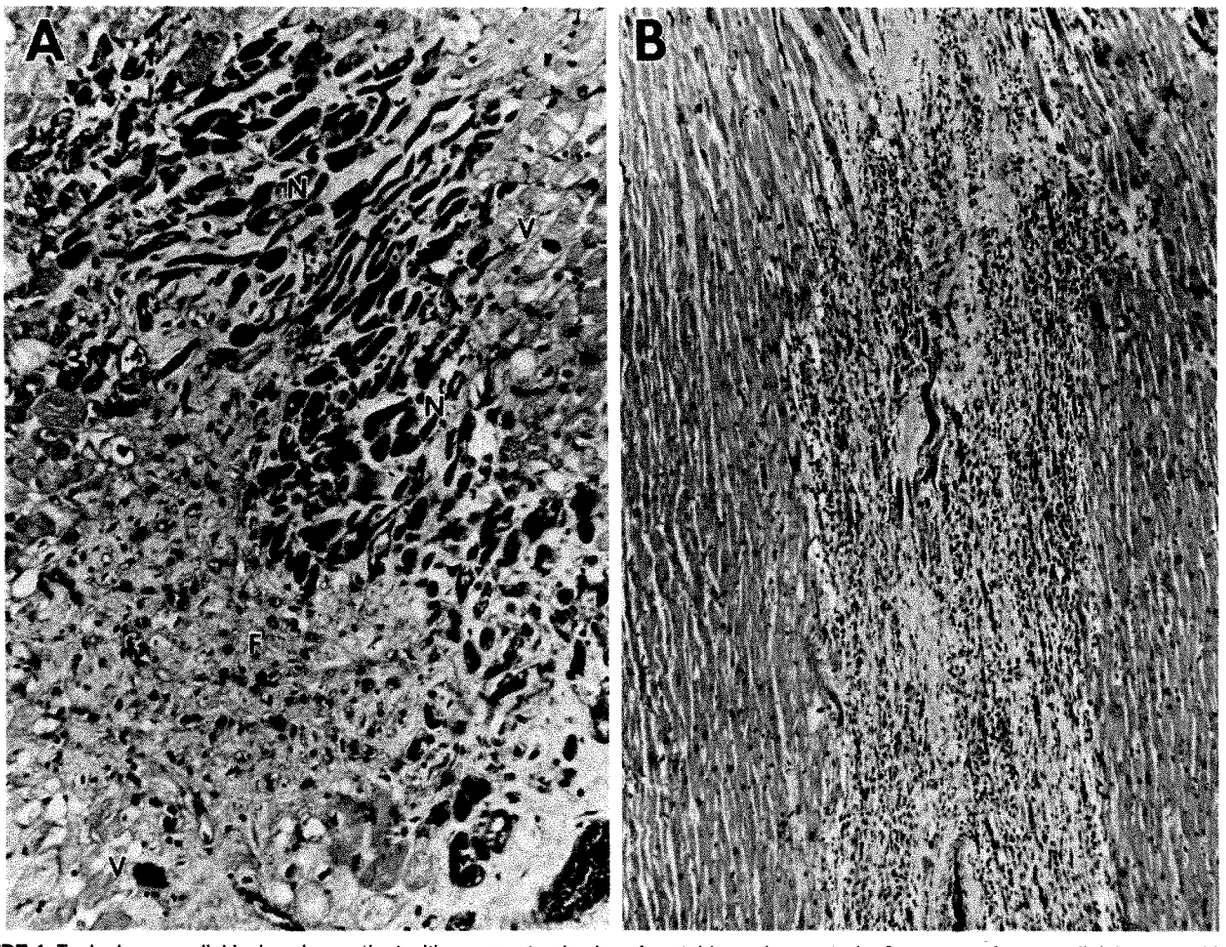

FIGURE 1. Typical myocardial lesions in a patient with recurrent episodes of unstable angina pectoris. **A,** an area of myocardial damage with foci of acute coagulation necrosis (N), early replacement fibrosis (F) and vacuolated muscle cells (V) with hydropic and myocytolytic degeneration. **B,** subacute lesion composed of granulation tissue with a few unresorbed necrotic muscle cells. (Hematoxylin-eosin ×140.)

lesions and multiregional or circumferential myocardial infarcts, the recent coronary lesions were associated with extensive severe multivessel coronary atherosclerosis, usually with one or more old occlusions. Severe and extensive coronary atherosclerosis also was present in one case in association with an acute inferior myocardial infarct and an acute occlusive thrombus of the left anterior descending coronary artery ("paradoxical infarction").

Chronic myocardial changes: Chronic cardiac alterations associated with gross transmural infarcts, gross subendocardial infarcts and multifocal microinfarcts, with and without recent coronary occlusions, are presented in Table III. Cardiac hypertrophy (heart weight greater than 400 g) was present with 85 percent of the recent myocardial infarcts, including 86.9 percent of infarcts with recent coronary occlusions and 82.1 percent of infarcts without recent occlusions. A previous myocardial infarct or patchy fibrosis, or both, occurred before 70 percent of the recent infarcts, including 60.7 percent of infarcts with and 84.6 percent of infarcts without recent associated occlusions ($p = 0.02$).

Chronic coronary arterial changes: Severe coronary arterial narrowing (greater than 75 percent of luminal area) by old atherosclerotic plaques involved none of the major coronary arteries with 4 recent infarcts, one coronary artery with 15 infarcts, two coronary arteries with 16 infarcts and three to five coronary arteries with 65 infarcts. The incidence of vessel involvement by severe atherosclerosis was similar in cases with and without a recent occlusive lesion. Two cases were associated with significant, extensive and severe intramural coronary artery disease. In one case severe atherosclerosis of the extramural arteries was present and in another the extramural arteries were patent; a recent coronary occlusive lesion was not present in either case. There was a significant difference ($p < 0.001$) in the types of myocardial infarcts in the cases with and in the cases without coronary occlusion; regional anterior and inferoposterior infarcts occurred more frequently in the presence of an acute coronary occlusion, and multiregional gross infarcts and multifocal microinfarcts occurred more frequently in the absence of a recent coronary occlusion.

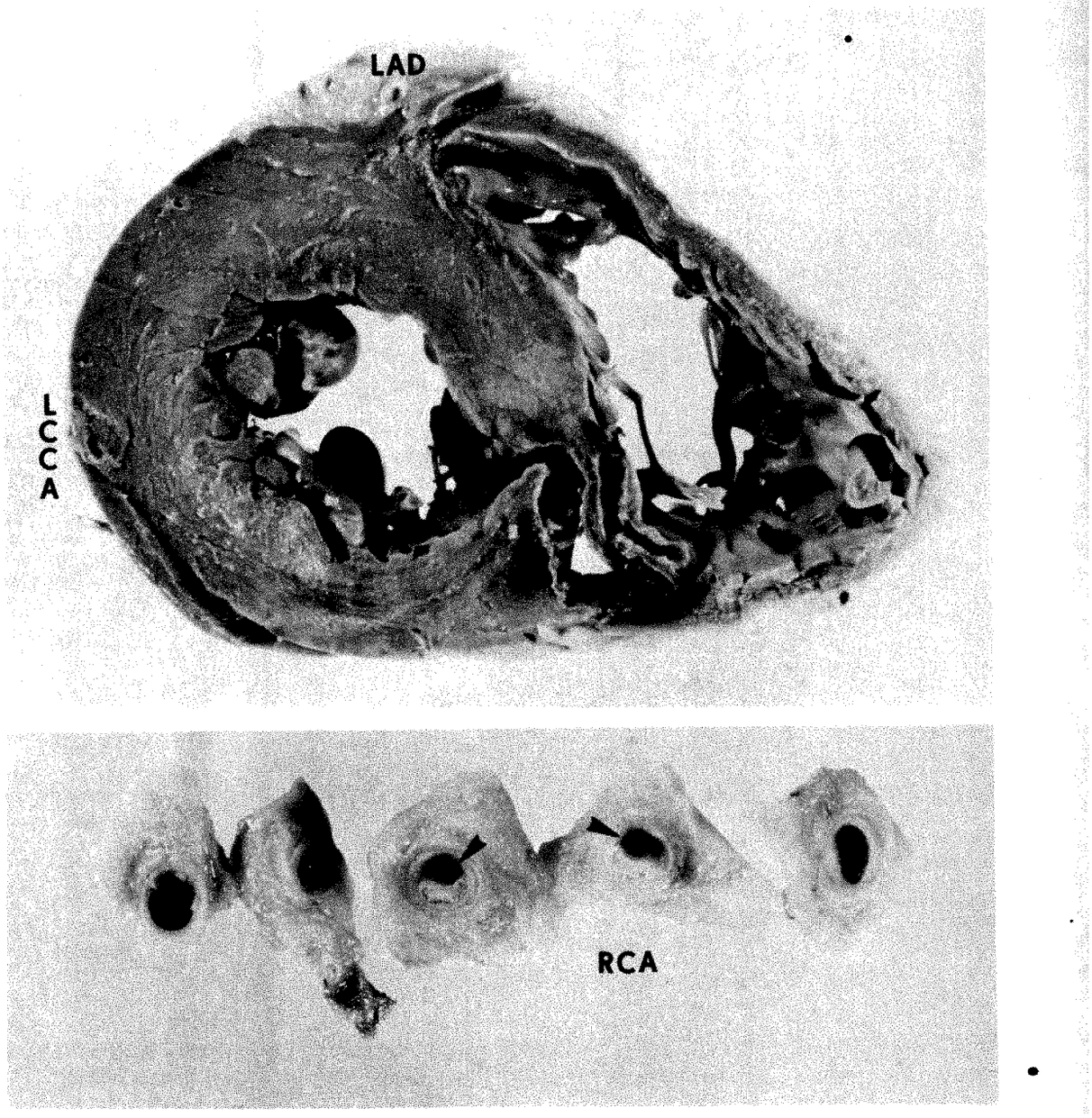

FIGURE 2. Two day old inferoposteroseptal transmural myocardial infarct with ventricular septal rupture in a 51 year old woman. The left anterior descending coronary artery (LAD) shows moderate atherosclerosis and the left circumflex coronary artery (LCCA) is free of disease. At the site of the only severely stenotic plaque in the right coronary artery (RCA), there is an occlusive thrombus adjacent to an area of major plaque hemorrhage. The **arrows** indicate a plane of demarcation formed by a thin strand of attenuated and eroded plaque capsule between the centrally located thrombus and the peripheral plaque hemorrhage (see Fig. 3). Thrombus is also located immediately proximal and distal to the plaque. More distal segments of the artery do not have significant atherosclerosis or thrombus.

Clinical Findings

Clinical diagnosis of myocardial infarction and acute coronary insufficiency: The 100 recent myocardial infarcts occurred in 83 patients. Of the 83 patients, 55 had one, 8 had two and 1 had three gross infarcts; 7 had one gross infarct and a separately identified region of multifocal microinfarction, and 12 had multifocal microinfarcts. Of the 81 gross myocardial infarcts in 71 patients, 70 infarcts (86.4 percent) were associated with a clinical diagnosis of acute myocardial infarction; the remaining 11 lesions (13.6 percent) were not associated with a suspected or established clinical diagnosis of infarction. Eight of the 11 latter lesions were gross subendocardial infarcts. The multifocal microinfarcts occurred in 19 patients who experienced one or more episodes of acute coronary insufficiency within 3 months of death. The clinical diagnoses were unstable angina pectoris in 13 patients, recurrent severe angina

FIGURE 3. Same case. Histopathologic features of the acute right coronary occlusion shown in Figure 2. The coronary plaque shows superficial erosion (E) with disruption of fibrous tissue and hemorrhage in the plaque and thrombus (T) in the lumen. (Hematoxylin-eosin ×144, reduced by 5 percent.)

pectoris in 5 and recurrent painless acute pulmonary edema in 1 patient with diabetes mellitus.

Previous cardiovascular disease and predisposing factors: Clinical cardiovascular alterations occurring before the clinical onset of myocardial infarction are shown in Table IV. A history of prior angina pectoris was noted in 68 percent and a history of documented systemic hypertension in 48 percent. The incidence of these two findings was similar with infarcts with and without associated coronary occlusion. Clinical conditions predisposing to reduced coronary perfusion were diagnosed before the onset of infarction in 40 percent of cases. These alterations consisted of chronic or recurrent congestive heart failure, aortic stenosis and septic or toxic shock. Such alterations were documented before the occurrence of 61.5 percent of infarcts without and only 26.2 percent of infarcts with associated recent occlusions ($p < 0.001$). Among the 39 infarcts without associated recent occlusions, the incidence rate of predisposing hemodynamic alterations was 76.4 percent for gross subendocardial infarcts, 60.0 percent for gross transmural infarcts and 47.1 percent for multifocal microinfarcts. One of the infarcts developing in the absence of a history of a predisposing generalized hemodynamic alteration or a recent coronary occlusive lesion occurred in the only patient in the series with a history of Prinzmetal's variant angina pectoris.

Clinical course: Major features of the clinical course after the clinical onset of myocardial infarction are shown in Table V. Early onset (usually within 24 hours) of progressive and fatal cardiac pump failure occurred in 41 percent of cases, including 29 (47.5 percent) of 61 infarcts with and 12 (30.8 percent) of 39 infarcts without associated recent coronary occlusions ($p = 0.15$). Cardiac pump failure was manifested by hypotension, decreased urinary output and signs of peripheral vasoconstriction with variable degrees of pulmonary congestion. Other syndromes of impaired cardiac output included late onset pump failure and chronic congestive heart failure. The clinical syndromes of cardiac congestive or pump failure were associated with 55 percent of infarcts including 39 (63.9 percent) of 61 infarcts with and 16 (41.0 percent) of 39 without associated recent coronary occlusion ($p = 0.04$). The other 45 infarcts, including 22 of 61 infarcts with and 23 of 39 without associated recent occlusion, were not directly associated with prominent clinical findings of cardiac congestive or pump failure. These 45 infarcts included 15 that were complicated by fatal arrhythmias and 30 that were followed by survival with subsequent death from a new infarct, postoperative acute pump failure or metastatic cancer. All postoperative patients included in this study were judged to have myocardial infarcts that clearly antedated the operative intervention.

Discussion

General Findings

This study has shown that (1) the degree of chronic coronary atherosclerosis does not have a constant relation with the occurrence of acute episodes of ischemic heart disease, although most acute events occur in the setting of significant triple vessel disease; (2) clinical acute coronary insufficiency frequently is associated with multifocal myocardial necrosis in the absence of an acute coronary occlusive lesion; (3) transmural myocardial infarcts are associated with a much greater incidence of acute coronary occlusion than are subendocardial infarcts; (4) acute coronary thrombosis is frequently associated with acute alterations of the arterial wall characterized by plaque erosion, rupture and hemorrhage; and (5) the development of acute coronary thrombosis is not directly dependent on the occurrence of a generalized impairment of coronary perfusion, either before or after the onset of infarction.

A variety of factors involving differences in patient populations, case selection procedures and criteria used for subcategorization of cases undoubtedly influence the incidence of severe coronary atherosclerosis and acute occlusive lesions reported for various categories of ischemic heart disease.[1–28] However, the data indicate that the incidence of recent thrombosis is greatest with regional transmural infarcts, least with multifocal

or circumferential subendocardial infarcts and intermediate with regional subendocardial infarcts.[4,7-11,15,16,20,21,27] Our findings are in accord with previous data indicating a very large incidence of recent coronary thrombosis with regional transmural infarcts.[7,9,11,15,16,20,21] The findings with regard to coronary insufficiency are also in accord with previous data showing frequent occurrence of focal myocardial necrosis and fibrosis with various anginal syndromes.[3,14,17,19,25,26]

A complete picture of acute coronary artery disease also requires consideration of the major category of sudden death. This event typically occurs instantaneously or within minutes to a few hours of onset of

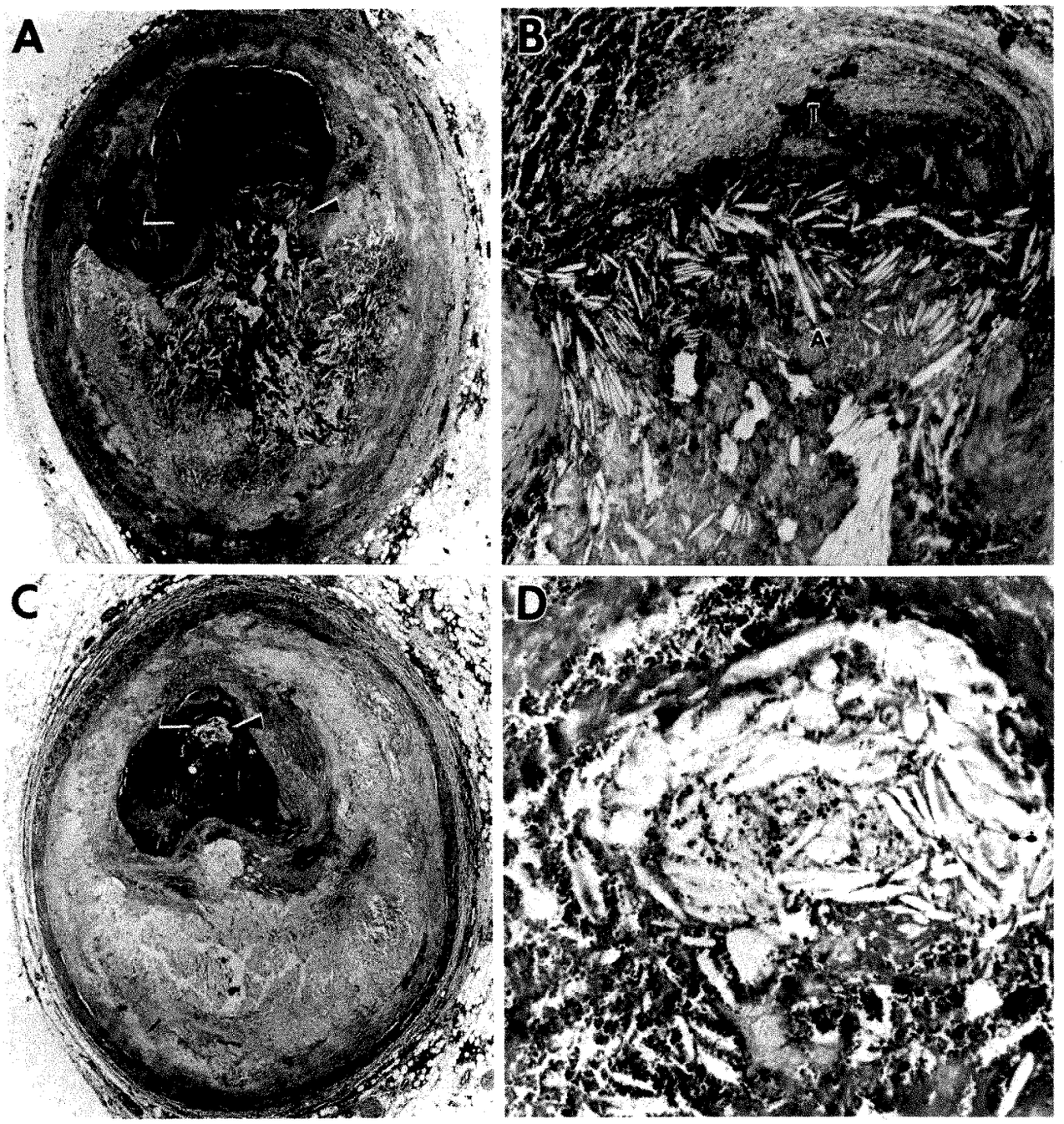

FIGURE 4. Histopathologic features of a coronary occlusion with plaque rupture, hemorrhage and thrombosis. **A,** the ruptured plaque shows separation of the capsule (**arrowheads**), outward displacement of plaque contents across the rupture site and communication with the overlying thrombus. **B,** higher magnification of the site of plaque rupture showing continuity between thrombus (T) and atheromatous (A) material of the plaque core. Note the abundant cholesterol crystals in the atheromatous material. **C,** a more distal segment of the artery shows atheromatous debris within the thrombus (**arrowheads**). **D,** higher magnification view of the atheromatous material within the thrombus. (Hematoxylin-eosin ×13.5 [**A**], ×57 [**B**], ×13.5 [**C**], ×144 [**D**].)

cardiac symptoms, usually in unhospitalized patients.[5,6,12,18,22–24] Previous clinicopathologic studies have shown that only a minority of patients with sudden cardiac death show evidence of discrete acute myocardial infarction or acute coronary occlusion.[5,6,12,18,22–24] The majority exhibit chronic coronary atherosclerosis and have no evidence of an acute coronary occlusion or a discrete myocardial infarct. However, they may have multifocal microscopic foci of hyperacute muscle cell injury characterized by myofibrillar hypercontraction.[18,24] These patients also frequently exhibit microthrombi and platelet aggregation in epicardial and intramural coronary arteries. However, the incidence of these lesions may not be substantially different in patients with sudden coronary death compared with that in patients with chronic coronary disease.[41–43]

Role of Coronary Thrombosis

Arguments for secondary role of coronary thrombosis in acute myocardial infarction: Variation in clinical and pathologic findings has led to differing interpretations of the role of acute coronary thrombosis and related lesions in the genesis of acute ischemic heart disease.[5–10,15,16,20,21,27,44–52] Several observations have been advanced to support the concept that coronary thrombi develop independently of acute myocardial infarction or as purely secondary phenomena relatively late in the course of acute myocardial infarction.[10,27,44–49] These observations include (1) the occurrence of coronary thrombosis without the development of acute myocardial infarction; (2) the small incidence of coronary thrombi in cases of sudden death; (3) the occurrence of myocardial infarction without demonstrable acute coronary thrombosis; (4) the greater incidence of coronary thrombi with relatively large infarcts and transmural infarcts, interpreted as indicating that larger infarct size predisposes to thrombus formation; (5) the large incidence of coronary thrombi with infarcts complicated by cardiogenic shock or severe congestive heart failure; (6) the frequent formation of coronary thrombi at sites of severe atherosclerotic narrowing in arteries that also frequently exhibit long stenotic segments, severe distal disease and prominent collateral anastomoses; and (7) results of initial radiofibrinogen tracer studies showing that coronary thrombi can incorporate tracer injected intravenously several hours after the clinical onset of myocardial infarction.[53,54]

Arguments in favor of a secondary role for coronary thrombi were stronger when available evidence suggested that patients with sudden cardiac death died at an early stage in the evolution of acute myocardial infarction.[10] However, more recent studies have indicated that the sudden cardiac death syndrome and acute myocardial infarction are separate entities with different pathogeneses. Most patients resuscitated from sudden cardiac collapse do not exhibit evidence of major myocardial infarction.[55–57] The sudden cardiac death syndrome appears to result from a primary arrhythmia, usually ventricular fibrillation, induced by an acute ischemic event not usually involving a major coronary thrombosis or by recurrent ventricular arrhythmia occurring in the setting of chronic coronary artery disease.[55–59] A corollary of this concept is that primary arrhythmogenic sudden cardiac death and sudden death induced by an arrhythmia during the course of acute myocardial infarction (secondary arrhythmia) are separate entities.

Arguments for a primary role of acute coronary thrombotic occlusion: Several observations strongly support the view that acute thrombotic occlusion generally exerts an important effect on the evolution of myocardial infarction.[7,15,16,20,21,51,52] Several postmortem studies, including this study, have shown (1) an association between acute coronary occlusion and regional myocardial infarcts, and a very large incidence of acute occlusion with regional transmural infarcts; (2) a spatial relation in most cases between the location of an infarct and an acute occlusion in the artery supplying the infarcted area; (3) a chronologic relation within the limits of the histologic method, between the age of the thrombi and the age of the infarcts; (4) lack of uniformity in the severity of atherosclerosis, including distal disease in arteries that manifest thrombi; and (5) the frequent association of coronary thrombi with the focal arterial lesions (plaque erosion, rupture and hemorrhage) that probably predispose to thrombus formation.[7,21,51,52,60–63]

Initial radiofibrinogen tracer studies suggested that thrombi formed relatively late in the course of infarction.[53,54] However, more recent studies have shown that radiofibrinogen becomes extensively incorporated into thrombi formed in experimental animals before the injection of tracer.[64,65] In addition, Fulton and associates[52,66] have reported that a radionegative central core can be demonstrated in most human thrombi, thus suggesting the initial occurrence of thrombus formation before injection of tracer.

Significance of Plaque Lesions Associated With Thrombi

Arguments have been advanced that coronary intimal plaque disruption and hemorrhage are produced artifactually by resuscitative efforts or by sectioning of the coronary arteries at autopsy. These arguments are contradicted by (1) the frequent association of plaque erosion, rupture and hemorrhage with occlusive thrombi, (2) the frequent association of plaque disruption with plaque debris admixed in the thrombus, and (3) by the histologic appearance of ruptured plaques suggesting disruption due to a force exerted from within the vessel wall and directed toward the lumen.[7,15,20,21,51,52,60–63] The relatively large plaque hemorrhages associated with plaque disruption and thrombosis appear to be derived primarily from influx of blood across the damaged plaque surface. In contrast, small petechial or microscopic hemorrhages frequently develop in plaques by extravasation from intraplaque vessels without associated plaque disruption and thrombosis.[63,67] In our study, the incidence rate of

plaque lesions with thrombi was 67.6 percent for infarcts aged 3 weeks or less. The apparent incidence rate decreased to 20 percent with older infarcts, probably because organization and healing made identification of these lesions more difficult. Other investigators, using serial section techniques, have found a very high incidence rate, usually greater than 90 percent, of plaque erosion and rupture associated with major plaque hemorrhages and acute coronary thrombi.[7,20,21,60–63]

Pathogenesis and causative factors: Plaque erosion, ulceration, rupture and thrombosis commonly occur in atherosclerotic vessels including the aorta and other diseased arteries in addition to coronary arteries. There probably is a variable and diverse pathogenesis for erosion, ulceration and rupture of plaques.[20,21,31,43,63] These phenomena typically involve plaques with prominent atheromatous cores and thin fibrous capsules (soft plaques or atheromas). Causative factors may involve chronic hemodynamic trauma, inflammatory or chemical injury to endothelium and subendothelial tissue, increased intraplaque pressure due to infiltration of blood and, finally, vasospasm in coronary arteries and other muscular arteries. In a recent study, evidence of coronary spasm was found in 6 (40 percent) of 15 patients with coronary atherosclerosis and acute myocardial infarction.[31] The histologic appearance of diseased coronary arteries indicates that an anatomic substrate for spasm frequently is present in the form of segments of well preserved medial smooth muscle in areas with eccentric plaques or less severe disease. However, uncertainty remains regarding the frequency and exact point at which coronary spasm occurs in the sequence of damage to the vessel wall, acute coronary occlusion and evolution of myocardial infarction.[36] Factors involved in this sequence may involve alterations in chemical mediators, such as prostacyclin and thromboxane A_2, platelet aggregation, a local or systemic increase in catecholamines, autonomic neural influences and systemic or local alterations in the clotting and fibrinolytic systems.[68–77]

Significance of Clinical Observations

Clinical correlations have indicated that myocardial infarction can have a variable pathogenesis. Clinical observations have also suggested an important role for acute coronary occlusion in the genesis of many myocardial infarcts. Pertinent clinical observations in this study were: (1) the high incidence rate of hemodynamic factors predisposing to reduced coronary perfusion with infarcts unassociated with coronary thrombi, in accord with the early observations of Friedberg and Horn[2]; (2) the low incidence of such predisposing factors with infarcts associated with coronary thrombi; and (3) the occurrence of coronary thrombi in the presence or absence of cardiac pump failure or congestive failure after onset of infarction. Walston et al.[8] reported a very large incidence of coronary thrombi with myocardial infarction complicated by cardiogenic shock and a small incidence of thrombi with infarcts unassociated with shock. However, other investigators[9,11] reported that smaller infarcts without shock and larger infarcts with shock had a similarly large incidence of coronary thrombi. Thus, the clinicopathologic findings in this and previous[9,11] studies negate the argument that formation of coronary thrombi can be explained on the basis of a generalized impairment in coronary perfusion after the onset of myocardial infarction.

Myocardial Versus Coronary Factors in Myocardial Infarction

Additional considerations have been raised regarding the pathogenesis and effects of acute coronary thrombosis. Some investigators[27,45–47,50] have emphasized that the potentially detrimental effects of an acute coronary occlusion can be counteracted by a coronary collateral system sufficient to maintain blood flow distal to an acutely occluded segment. A further proposal is that myocardial infarction is initiated by subendocardial ischemia resulting from some impairment in the myocardial oxygen supply/demand ratio that does not involve coronary thrombosis. In many cases, the important initiating factor may be a circulatory derangement that decreases coronary perfusion and elevates left ventricular end-diastolic pressure creating a hemodynamic vise in the subendocardium.[50] Vasospasm of small coronary arteries also may be an initiating or contributory factor.[35,48,49] The hypothesis has been advanced that increased vascular resistance in the ischemic or infarcted myocardium could lead to reduced flow and stasis in the arterial system supplying the region. This may be followed by thrombus formation at a site of maximal obstruction and possibly also by plaque rupture and hemorrhage.[27,45–49] Generalized impairment in coronary perfusion has been proposed as a major contributing factor in this process.[44] It has also been proposed that collateral flow around a stenotic segment could contribute to thrombus formation in addition to minimizing a major functional effect of the occlusion.[27,45–49] The latter argument has been linked to the observation that coronary bypass grafting can create a state of competitive flow that predisposes to thrombus formation at the anastomosis and in the proximal artery.[27] Thus, proponents of the extreme form of the myocardial hypothesis regard thrombosis as a frequent secondary event of little functional consequence in myocardial infarction.

The possibility that myocardial factors contribute to the evolution of infarction is intriguing. It is conceivable that some thrombi form without plaque disruption in extensively and severely stenotic arteries in response to increased myocardial vascular resistance and vascular stasis.[10] Experimental studies have shown that increased vascular resistance and reduced reflow develop in the necrotic subendocardium after 90 to 120 minutes of coronary occlusion in the dog.[78,79] However, the extreme form of the myocardial hypothesis is highly speculative. From this hypothesis, it is difficult to explain the variable occurrence of infarction without thrombosis and thrombosis without and with infarction. Postmortem studies have not provided an adequate

explanation for these phenomena on the basis of anatomic differences in extent of coronary collateral development.[45,46] However, there is general agreement that coronary collateral flow in some instances can compensate for acute occlusion so that no myocardial necrosis results.[3,4,27,45–52] Another reasonable conclusion is that variations in the extent of generalized coronary atherosclerosis and of coronary collateral flow influence whether an acute coronary occlusion is followed by no infarct, a subendocardial infarct or a transmural infarct.[3,4,51,52] The positive correlations between coronary occlusions and regional infarcts, transmural infarcts and infarct size[27] strongly suggest that an acute occlusion, typically in the form of a thrombus, usually acts as a major factor in determining the final extent of an evolving myocardial infarct. Furthermore, the frequent association of coronary thrombosis with plaque erosion, rupture and hemorrhage strongly suggests that the key initiating event in thrombus formation occurs in the coronary artery.

Conclusions

A broad perspective on the spectrum of acute ischemic heart disease directs major emphasis to the triggering mechanisms that initiate acute clinical events, including the sudden cardiac death syndrome and acute myocardial infarction with or without associated acute coronary occlusion. Earlier studies have clearly established that acute events can be precipitated by factors that increase myocardial oxygen demand or reduce cardiac or coronary reserve.[2–4] Recent studies[30–36,68–77] have suggested the potential importance of additional factors, such as platelet alterations, imbalance in the prostacyclin-thromboxane A_2 system and altered adrenergic function and the probable influence of these factors on induction of coronary arterial spasm. In this broader context, coronary thrombosis should not be considered in purely primary or secondary terms but as a contributing factor of frequently major importance in the evolution of the dynamic pathophysiologic events that constitute acute ischemic heart disease.

Certain observations related to coronary thrombosis appear important in the selection of patients for some forms of therapy such as anticoagulation and intracoronary administration of fibrinolytic agents.[80–83] These observations include the large incidence of coronary thrombosis with transmural infarcts, the variable incidence of thrombosis with subendocardial infarcts and its frequent association with plaque disruption. The characteristic clinicopathologic features of various ischemic heart disease syndromes also should be considered in the design and evaluation of studies dealing with pharmacologic interventions, definition of risk groups and development of prognostic criteria.

Addendum

De Wood and associates[84] reported clinical coronary arteriographic findings in 322 patients admitted within 24 hours of acute transmural myocardial infarction. The overall incidence rate of total coronary occlusion was 79.8 percent, with incidence rates of 85 to 87 percent within the first 6 hours of infarction and 65 to 68 percent at 6 to 24 hours. A substantial incidence rate of subtotal occlusion (greater than 95 percent narrowing) also was noted. In 79 patients who were undergoing emergency coronary bypass surgery, fresh thrombi were recovered from the coronary arteries of 57 (72.2 percent). Thus, the clinical findings of De Wood and associates[84] confirm the autopsy evidence of a very high incidence rate of occlusive coronary thrombosis with regional transmural infarction.

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Response of the Left Ventricle to Stress: Effects of Exercise, Atrial Pacing, Afterload Stress and Drugs

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A variety of tests are being utilized today to diagnose the presence of ischemic heart disease, assess the prognosis of myocardial and valvular heart disease and evaluate the effects of various pharmacologic agents on cardiac performance. This review summarizes the current evidence regarding the response of left ventricular performance and size to atrial pacing, afterload stress and various forms of exercise. The response in normal persons and in subjects with coronary heart disease is reviewed and, when applicable, the effects of various pharmacologic agents on exercise performance in these patient groups are examined.

In 1959, Rushmer et al.[1] noted that deficiencies in our basic understanding of accepted hemodynamic theories often are corrected with the introduction of new or improved techniques. Although this observation was made more than 2 decades ago in an article about the ventricular response to exercise in animal preparations, the comments are still applicable. It is agreed that the cardiac response to exercise and other forms of stress is complex, but only recently have contrast ventriculography, radionuclide angiography and echocardiography been applied to the heart under stress. In particular, left ventricular function and size can now be serially evaluated with either the radionuclide or the ultrasonic technique without important alterations in loading conditions.

The goal of this review is to discuss the effects of exercise, atrial pacing, afterload stress and isoproterenol on left ventricular size and function in normal subjects and patients with coronary heart disease. The specific effects of supine and erect bicycle exercise, treadmill exercise and isometric (handgrip) exercise will be considered.

Exercise

Supine Bicycle Exercise (Fig. 1)

Normal subjects: End-diastolic volume at rest is near maximum when a subject is reclining, smaller when he is sitting and smallest when he is standing.[2–4] Thus, during supine exercise, only occasionally do alterations in preload play an important role in the normal subject.[4–10] During exercise, myocardial shortening increases, end-systolic volume declines and left ventricular end-diastolic pressure increases slightly.[5,6,10] Additionally, systolic blood pressure and left ventricular systolic pressure increases,[5,6,11] but there is little change in the diastolic pressure-volume relation.[6] In most studies, left ventricular ejection fraction increases with exercise in 80 to 100 percent of normal subjects,[4–6,11–14] although this change has not been found by all investigators[15] and may vary with patient populations[16] and the presence of other illnesses.[11,17] Similarly, right ventricular ejection fraction increases,[18,19] with little change in right ventricular end-diastolic volume.[20]

Patients with coronary artery disease: The presence of significant coronary heart disease alters these findings. Patients with ischemic disease, even in the absence of angina pectoris, are often unable to exercise to work loads or heart rates equal to those of normal control subjects.[7,11,13,18] Usually there is little if any increase in end-diastolic volume during exercise and an elevation in end-diastolic pressure, with

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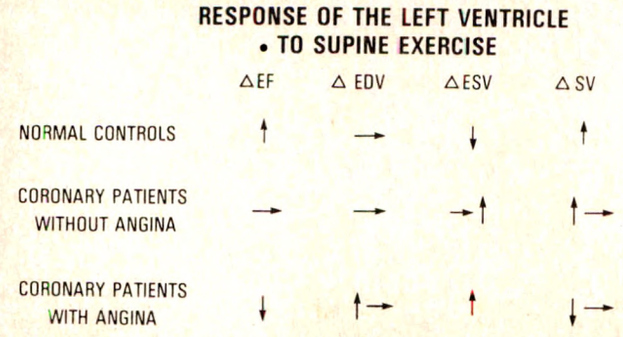

FIGURE 1. Response of ejection fraction (EF), end-diastolic volume (EDV), end-systolic volume (ESV) and stroke volume (SV) to supine exercise. ↑ = an increase; → = little change; ↓ = a decrease.

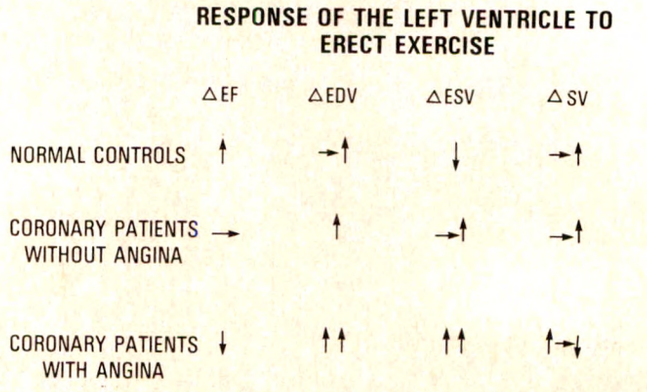

FIGURE 2. Hemodynamic responses to erect bicycle exercise. Abbreviations and symbols as in Figure 1.

no change or an increase in end-systolic volume.[5–7,11,21] Wall motion disorders may appear. If angina is produced during supine exercise, there may be modest to marked ventricular dilatation, with a greater increase in end-systolic volume and a reduction in ejection fraction.[5–7] Many of these exercise-induced abnormalities in left ventricular size and function may be reversed by pretreating the patient with sublingual nitroglycerin or nitroglycerin paste prior to the exercise study.

Erect Bicycle Exercise (Fig. 2)

Hemodynamic effects: The published data on erect bicycle exercise are fewer than on supine exercise, as might be expected from the technical ease with which supine studies may be performed and the difficulty with imaging the erect, exercising patient. Sitting erect produces smaller resting end-diastolic volumes than those obtained by lying flat.[2,22,23] Similarly, left ventricular end-diastolic pressure, pulmonary capillary wedge pressure, cardiac index and stroke volume index are less in the erect than in the supine position.[24,25] In the normal subject during erect exercise, cardiac index and stroke volume index both increase, as do systolic pulmonary capillary wedge and left ventricular end-diastolic pressures.[24] In patients with ischemic disease, pressures increase even more markedly during exercise. In subjects who experience angina during exercise in the supine position, cardiac index and stroke volume index are similar to those of supine values at rest, whereas in the erect position, although angina develops and pressures increase, cardiac index and stroke volume index may still be greater than at rest.[25]

Radionuclide angiography: A variety of recent noninvasive studies have analyzed the response of ventricular size and function to erect exercise.[4,26,27] Rerych et al.,[26] using first-pass radionuclide angiography, evaluated both normal subjects and patients with coronary heart disease during erect bicycle exercise. They found that during exercise the heart rate doubled, the cardiac output tripled and the ejection fraction increased in normal subjects. In addition, there was a minimal increase in end-diastolic volume and a marked reduction in end-systolic volume. In patients with coronary disease, the ejection fraction tended to remain unchanged or decreased with exercise, in association with an increase in end-diastolic and end-systolic volumes. They found that the greater the severity of the coronary disease, the more marked the ventricular dilatation.

Echocardiography: In an echocardiographic study involving semi-supine exercise, Weiss et al.[27] found that marked ventricular dilatation occurred with exercise, with little change in end-systolic volume. Crawford et al.[4] were unable to confirm this degree of dilatation in their supine or erect patients. At present the data from these angiographic and echocardiographic studies,[4,26,27] indicate that during erect exercise, normal subjects have an increase in ejection fraction due to a modest reduction in end-systolic volume, perhaps some degree of ventricular dilatation, and an increase in stroke volume. Patients with coronary heart disease manifest some degree of left ventricular dilatation, along with an increase in end-systolic volume and stroke volume, and a decrease or little change in ejection fraction. End-diastolic volume may not prove to be as important during protracted exercise as during brief bursts of exertion.[28]

Regional pulmonary and cardiac blood volumes: Using a multicrystal positron camera and ^{11}C-carboxyhemoglobin, Nichols et al.[29] examined the effects of upright exercise on regional pulmonary and cardiac blood volumes. In patients with single vessel coronary disease or normal coronary arteries, regional blood volume was unchanged in the upper and lower pulmonary lung fields during exercise, and total cardiac volume was reduced during stress. In patients with multivessel disease, blood volume increased in the upper and lower lung fields with exertion, in association with an increase in cardiac volume. A related study from Okada et al.[30] reported similar blood volume data from the pulmonary bed. Thus, the increase in left ventricular end-diastolic pressure during exercise leads to pulmonary congestion and increased pulmonary blood volume. With more widespread coronary disease, these findings become more prominent, and as might be expected, congestion more marked.

Treadmill Exercise and Upright Exercise

Animal studies: Because treadmill exercise involves fairly active exertion, and presents substantial difficulties with respect to pressure monitoring and cardiac imaging, few data during exercise are available in human subjects. A number of studies involving animals yield information that in all likelihood can be extrapolated to human subjects. Rushmer[31] reported that the most striking response to upright exercise in dogs was an increase in heart rate, with modest increase in stroke volume (rarely exceeding 30 percent of resting values). In addition, left ventricular diameter decreased. Barger et al.[32] found a linear relation between oxygen consumption and cardiac output during graded exercise, and described a variable stroke output response using that technique. Horwitz et al.[33] found similar results in exercising dogs. These data suggested that increased stroke volume is not a necessary feature of standing exercise. Vatner et al.[34] analyzed the left ventricular response to severe exercise by telemetry of direct cardiac measurements. They found that with severe exercise in tethered dogs, stroke volume increased 30 percent, heart rate tripled and thus cardiac output quadrupled. Left ventricular end-diastolic pressure rose (200 percent), but end-diastolic dimension increased only slightly (less than 1 percent) and end-systolic dimension decreased a similarly small amount. Thus the major change in cardiac output was related to heart rate rather than to substantial alterations in cardiac size.

Hemodynamic response in human subjects: Information in human beings about the hemodynamic response to treadmill exercise is mostly indirect. The major physiologic variables that have been measured included maximal oxygen consumption, heart rate, blood pressure, ventilatory volume and respiratory quotient.[35] Maximal oxygen consumption is the highest level of oxygen that an ambulatory person can extract, and equals cardiac output times the arteriovenous oxygen difference. In general, maximal arteriovenous oxygen difference is a constant[36]; thus, within each person, maximal oxygen consumption reflects cardiac output, and thus the limits of that person's cardiovascular system. Although the data are predominantly inferential, increases in heart rate appear to produce the most substantial part of the increase in cardiac output and maximal oxygen uptake. Stroke volume in all likelihood increases slightly.

Radionuclide angiographic studies: In a recent radionuclide study, Battler et al.[37] evaluated ejection fraction changes in the immediate recovery period after exercise. In their study, both normal subjects and patients with coronary disease had a normal ejection fraction before exercise. Additionally, in the immediate recovery period (2 to 4 minutes after completion of the exercise study) normal subjects had an increase in ejection fraction over the resting supine ejection fraction (mean ± standard error of the mean 0.61 ± 0.03 to 0.78 ± 0.06), which remained elevated even 10 minutes after completion of the study (0.73 ± 0.05). Patients with coronary artery disease had a mean post-treadmill ejection fraction that was insignificantly greater than the value at rest (0.59 ± 0.06 to 0.64 ± 0.06) and that returned to the baseline value by 10 minutes after the study. These subjects also underwent supine exercise bicycle exercise, in which the peak exercise ejection fraction was lower for both the normal subjects and patients with coronary disease. Unfortunately, the volume response was not evaluated in this study.

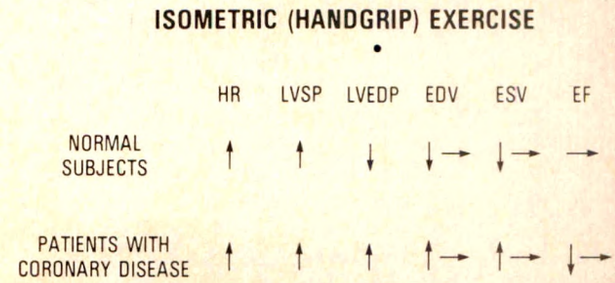

FIGURE 3. Hemodynamic responses to handgrip exercise. HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVSP = left ventricular systolic pressure; other abbreviations and symbols as before.

Obtaining radionuclide or echocardiographic data during treadmill exercise is practically impossible. Newer radionuclide monitoring devices that may be worn rather than positioned[38] would be of inestimable value in making such analyses more feasible.

Isometric (Handgrip) Exercise (Fig. 3)

Sustained muscular activity directed against an immobile object has been of significant value in providing a reproducible method for producing circulatory alterations directed at stressing the heart. Handgrip exercise is the most convenient and popular form of this type of stress.

Flessas et al.[39] used contrast ventriculography to evaluate the response of left ventricular volume and pressure to handgrip exercise. Normal persons manifested an increase in heart rate and systemic and left ventricular systolic pressures, together with a decrease in end-diastolic pressure, end-systolic volume and stroke volume. End-diastolic pressure declined; cardiac output and ejection fraction increased slightly. A similar study[40] using echocardiography in normal adolescents revealed little change in cardiac volumes and ejection phase indexes during handgrip exercise. Cardiac output increased because of an increase in heart rate. In patients with coronary heart disease, the response is variable, although most patients manifest new wall motion abnormalities[41] or other hemodynamic disturbances.[39,42–44] Most patients with coronary disease also have marked increases in left ventricular systolic and diastolic pressures, with reductions in cardiac volumes and often ejection fraction as well. In a study of patients after cardiac surgery, Savin et al.[45] found that handgrip exercise induced a slight reduction in ejection phase indexes along with a slight increase in end-diastolic and end-systolic volumes. These changes were more marked in subjects with an innervated than in those with a denervated heart, probably in part because of the lesser increase in heart rate in the latter patients.

Thus, although the data vary somewhat, handgrip exercise produces elevations in pressure and heart rate. In normal subjects, cardiac volumes decrease, ejection phase indexes in most studies remain unchanged and end-diastolic pressure declines. In patients with coronary disease, end-diastolic pressure increases, end-diastolic and end-systolic volumes increase or remain the same, stroke volume declines and ejection phase indexes decline or remain the same (Fig. 3). Wall motion abnormalities are either exacerbated or newly appear. This latter phenomenon is the most useful discriminator between normal subjects and patients with coronary disease.

Effects of Propranolol on Cardiac Performance During Exercise

Propranolol is one of the most commonly prescribed drugs in patients with cardiovascular disease. To provide an overall picture of its effect, I will review it here as a separate entity rather than separately with each exercise section.

The mechanisms by which beta adrenergic blockade provides relief of angina pectoris in patients with coronary heart disease have been extensively studied. Presumably, myocardial oxygen requirements are reduced, probably reflected by a reduction of heart rate-blood pressure product during exercise. In normal subjects, propranolol produces a reduction in heart rate and blood pressure; left ventricular dilatation occurs, but there is no change in myocardial shortening.[46,47] Similar results are seen in patients with coronary disease.[48–50]

Supine exercise: During supine exercise in normal subjects, heart rate was slower, blood pressure lower, left ventricular dimensions larger and percent shortening reduced.[46] Similar results were seen using radionuclide angiography.[50,51] The response in patients with coronary heart disease is somewhat more complicated. Battler et al.[49] analyzed the ejection fraction response to exercise in patients who manifested angina and electrocardiographic evidence of ischemia (greater than 1 mm S-T depression) during both treadmill and supine bicycle exercise. They found that propranolol reduced both heart rate at rest and during exercise, blood pressure during exercise and rate-pressure (double) product both at rest and during exercise. Resting ejection fraction remained unchanged, but the peak exercise ejection fraction was higher during treatment. Wisenberg et al.[51] found little change in peak exercise ejection fraction in patients with coronary artery disease after treatment with propranolol, although it was not clear if these patients manifest ischemia during exercise. Rainwater et al.[52] reported improvement in exercise perfusion and function in patients with reversible ischemia, though not in patients with previous infarction. Both Battler[49] and Rainwater[52] and their co-workers suggest propranolol may improve regional myocardial perfusion. Intravenous propranolol has a more marked negative inotropic effect, which can be seen at rest and during supine exercise in patients with coronary disease.[53] At present, few data are available on the volume response to supine exercise in patients with ischemic disease on and off oral propranolol.

Erect bicycle or treadmill exercise: Similar to supine exercise, during either erect bicycle or treadmill exercise, the most consistent effect of oral propranolol was a reduction of rest and exercise pressure-rate products, a slowing of heart rate, and an increase in resting stroke volume.[54] Using first-pass radionuclide angiography, Port et al.[55] evaluated the left ventricular response to erect bicycle exercise in normal subjects pre- and post-administration of oral propranolol (320 mg/day) for 2 days. After propranolol administration, cardiac output and ejection fraction was reduced at rest. During exercise, heart rate, systolic blood pressure, ejection fraction and cardiac output were lower and end-systolic volume higher than at comparable control stages during exercise. End-diastolic volume was also slightly greater at rest and peak exercise after propranolol. Few data are available regarding the response of patients with ischemic heart disease in the erect position to either intravenous or oral propranolol.

Atrial Pacing (Fig. 4)

Normal subjects: Increases in heart rate represent a positive inotropic stimulus, independent of other factors influencing ventricular performance such as the autonomic nervous system.[56–58] In both animal and human studies,[59] velocity ejection phase indexes increase with increases in (paced) heart rate. In this latter study, DeMaria et al.[59] found that fractional shortening declined during atrial pacing in normal subjects. Similar results were reported by Krayenbuehl et al.,[60] who found that ventricular volumes declined during atrial pacing in normal control subjects, along with little change in ejection fraction. Velocity indexes in this study increased. In a radionuclide study, Tzivoni et al.[61] reported a small insignificant increase in ejection fraction during atrial pacing in normals. The pacing rates in the latter study was greater than in the previously mentioned studies. In all studies involving normal subjects and patients with coronary artery disease, little change was found in cardiac output, systemic arterial pressure and peripheral vascular resistance. Analysis of regional shortening velocities demonstrated increases in regional contraction in normal subjects during pacing.

Patients with ischemic heart disease: In these patients ejection fraction decreases or remains un-

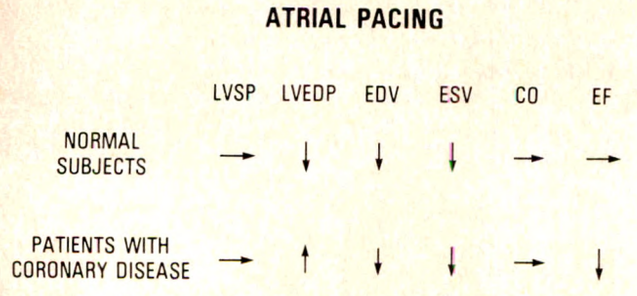

FIGURE 4. Hemodynamic response to atrial pacing. CO = cardiac output; other abbreviations and symbols as before.

changed[60–64] and regional wall motion is modestly altered.[60] If ischemia is produced, volumes may not decrease as markedly,[62,63,65] and end-diastolic pressure may increase.[61,62,65] Ischemia produces regional wall motion abnormalities,[63–65] although subjects with normal coronary arteries may also manifest septal wall motion abnormalities at higher pacing rates.[64] Studies in dogs with experimental coronary stenosis indicate that pacing-induced regional dysfunction persists in the post-pacing period. Later in a study involving patients with ischemic heart disease, Ricci et al.[66] found that, after pacing, control segments had greater regional shortening (when compared with values at rest), whereas myocardial regions supplied by stenotic vessels demonstrated reduced regional shortening. More than 90 percent of segments in compromised regions deteriorated, whereas 85 percent of segments in normal regions improved.

Thus, atrial pacing results in a reduction in cardiac size in normal subjects, with little change in ejection fraction, cardiac output or peripheral vascular resistance. Velocity indexes increase. In patients with ischemic heart disease, ventricular volumes decline, ejection fraction decreases or remains unchanged (although velocity indexes may not) and new wall motion abnormalities may appear, particularly immediately after pacing. In addition, end-diastolic pressure increases. Cardiac output does not change because stroke volume declines in proportion to the increase in heart rate.

Afterload Stress

Normal subjects: Many investigators have both recommended and investigated the use of altered systemic arterial pressure as a means of examining the contractile reserve of the left ventricle.[67–71] In normal subjects, with elevation of arterial pressure, a shortening velocity and isovolumic indexes of cardiac performance are reduced and end-diastolic and end-systolic volumes increase.[72–74] The predictability and reproducibility of these changes have been utilized to examine the effects of pharmacologic agents on left ventricular performance.[46,75,76] In association with ventricular dilatation, end-diastolic pressure[74] and cardiac output[72] increase.

Patients with noncoronary heart disease: Relatively little information is available in patients with coronary heart disease. In patients with noncoronary heart disease, increases in left ventricular and systemic pressure produce reductions in ejection phase indexes of left ventricular performance and increases in end-diastolic and end-systolic volumes. Both peak and mean wall stress increase.[77] It has been suggested that patients with chronic aortic insufficiency may be classified into subgroups depending on their response to pressure stress.[71] In one subgroup, an increase in pressure produced an increase in stroke work index and a modest reduction in ejection fraction. In the second group, the stroke work index declined with elevations in arterial pressure, usually with a reduction of resting ejection fraction to below 0.50. These patients were postulated to have latent or subclinical disturbances in contractile reserve.[71] Various studies involving other cardiac diseases in adults and children have previously been described,[78–81] none yielding as much clinical information as the study involving subjects with aortic insufficiency.

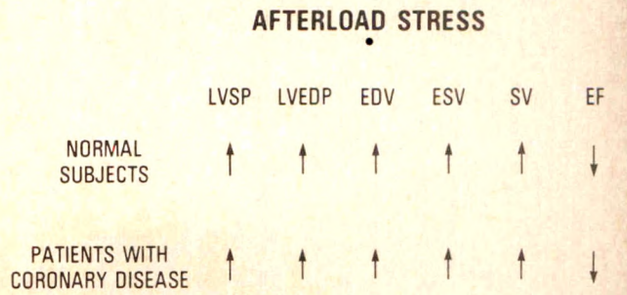

FIGURE 5. Hemodynamic responses to elevation in systemic arterial pressure by pharmacologic infusions. Changes in both patients and normal subjects are similar; however, as might be expected, alterations in end-diastolic volume (EDV) will vary with the volume status of the subject and the compliance characteristics of the individual ventricle. Abbreviations and symbols as before.

Patients with coronary artery disease (Fig. 5): Watkins et al.[82] evaluated both normal subjects and patients with coronary heart disease using equilibrium (gated) radionuclide angiography and phenylephrine. They found that the slope of the relation between systolic blood pressure and end-systolic volume was linear in all subjects ($r \geq 0.91$). End-systolic, end-diastolic and stroke volumes all increased with elevations in systemic pressure and ejection fraction, ejection rate and mean velocity of circumferential fiber shortening decreased. Normal subjects had a slightly greater slope to the end-systolic pressure/systemic volume relation, and a smaller Vo (theoretical end-systolic volume at an extrapolated zero pressure). However, they did not find the slope of the pressure/volume ratio superior to the resting ejection fraction in discerning normal subjects from patients with coronary heart disease. Thus, as previously suggested,[83] elevation in systemic pressure impedes systolic ejection, resulting in acute ventricular dilatation and reduced indexes of ventricular performance. The clinical utility of this technique is primarily restricted to examination of different pharmacologic agents at present.

Isoproterenol Stress

Comparison with exercise stress: The use of isoproterenol infusion to simulate exercise testing has been proposed to study pediatric patients and patients with valve stenosis.[84–86] Because isoproterenol is known to increase myocardial oxygen demand by enhancing myocardial contractile state and increasing heart rate,[87–90] it has been offered in conjunction with electrocardiographic monitoring as an alternate to electrocardiographic exercise testing.[91] Kuramoto et al.[92] found that in young men (mean age 23 years), isoproterenol infusions of 0.02 and then 0.09 μg/kg per min caused an increase in heart rate, cardiac index and stroke index similar to that caused by bicycle ergometric exercise of 50 and 100 watt seconds. Whereas bicycle exercise increased pressures, isoproterenol reduced

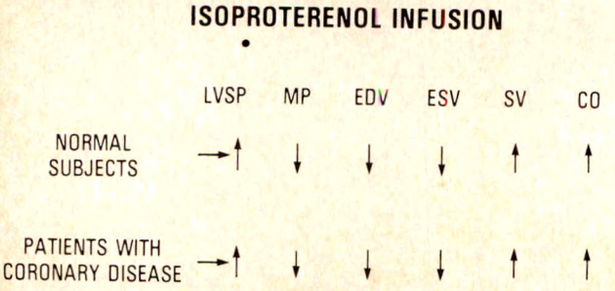

FIGURE 6. The hemodynamic response to isoproterenol infusion is displayed. MP = mean arterial pressure; other abbreviations and symbols as before.

diastolic and mean blood pressure. In an older patient population (mean age 73), the mean maximal bicycle exercise work load was 40 watt seconds. The changes in heart rate, blood pressure and cardiac performance were identical to those of the younger subjects at this work load. After isoproterenol, the increase in cardiac index and stroke index was less in old than in young men, showing either a decreased response to beta adrenergic stimulation or a limited reduction in the "afterload" effect of the drug due to the compliance characteristics of the vessels of the older patients.

Experimental effects: Battler et al.[93] evaluated the effects of isoproterenol on regional function in dogs with mild coronary stenosis. In the absence of an arterial occluder on a coronary artery, isoproterenol produced an increase in normal regional function. After partial occlusion, which produced no regional resting abnormalities, isoproterenol at small dosages (0.02 μg/kg per min) produced a significant decrease in wall thickening, which continued for a short time even after isoproterenol was discontinued, and returned to normal 5 minutes after the infusion was stopped. They concluded that with mild partial coronary stenosis that does not produce electrical or mechanical disturbances, small dose isoproterenol rapidly induces regional myocardial dysfunction and S-T alterations.

Clinical effects (Fig. 6): Isoproterenol is known to produce improvement in cardiac performance in patients with low cardiac output[94,95] because of its potent beta adrenergic effects, although this may not occur in patients with coronary heart disease.[96] Nonetheless, it has clearly been shown[97] that isoproterenol infusions induce: (1) a reduction in systemic vascular resistance; (2) an increase in cardiac output and index, and (3) an increase in ejection fraction with a reduction in both end-diastolic and end-systolic volumes. Similar results were seen in both normal subjects and patients with heart disease.

Conclusion

The ability of the ventricle to adapt itself to work requirements has allowed the creative investigator to stress the heart in any of a number of ways. These methods have included aerobic and anaerobic exercise as well as infusions of agents that alter preload, afterload and inotropic state. Most commonly, the aim has been to induce a degree of regional ischemia or left ventricular dysfunction that can be measured and quantitated by either surface electrocardiography, noninvasive cardiac imaging or intracardiac pressure and volume monitoring. The test, the agent and the measuring device all will vary depending on the original purpose of the protocol. It has been the goal of this review to clarify the basic ventricular responses to these interventions to facilitate these varied investigations, and to point the physician toward the intervention that is most likely not only to provide the answer to the clinical or physiologic question, but also to allow the question to be asked.

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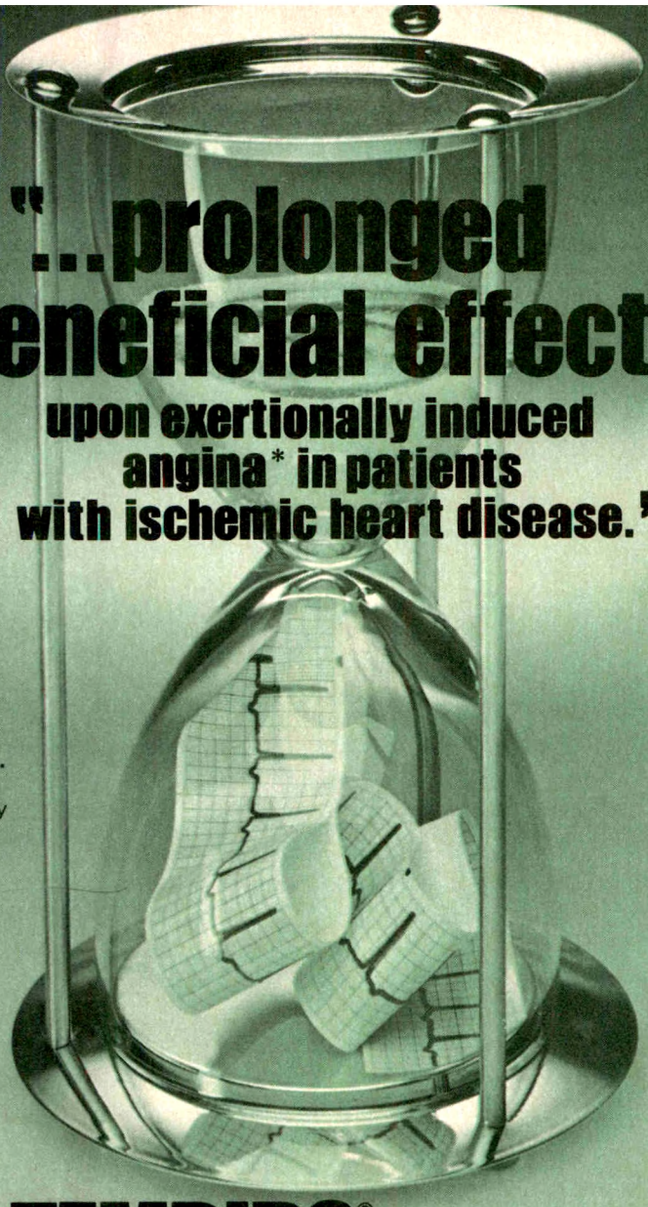

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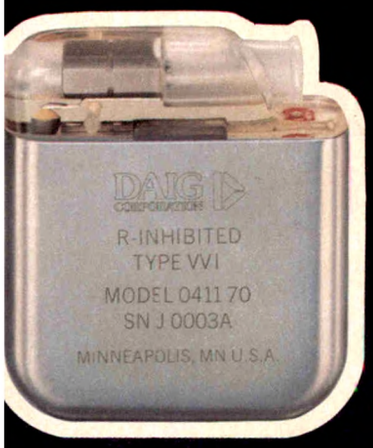

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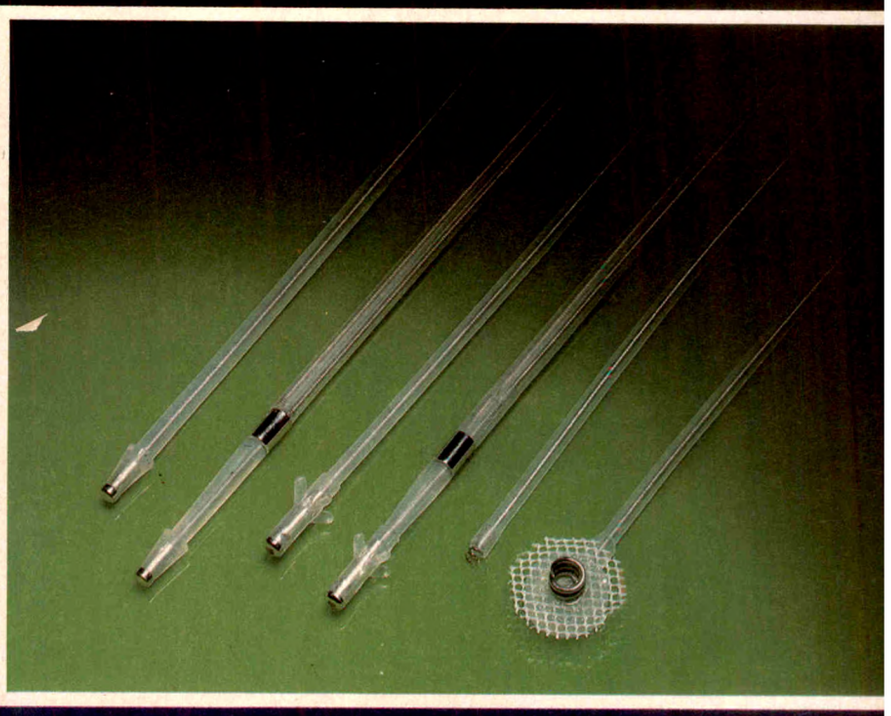

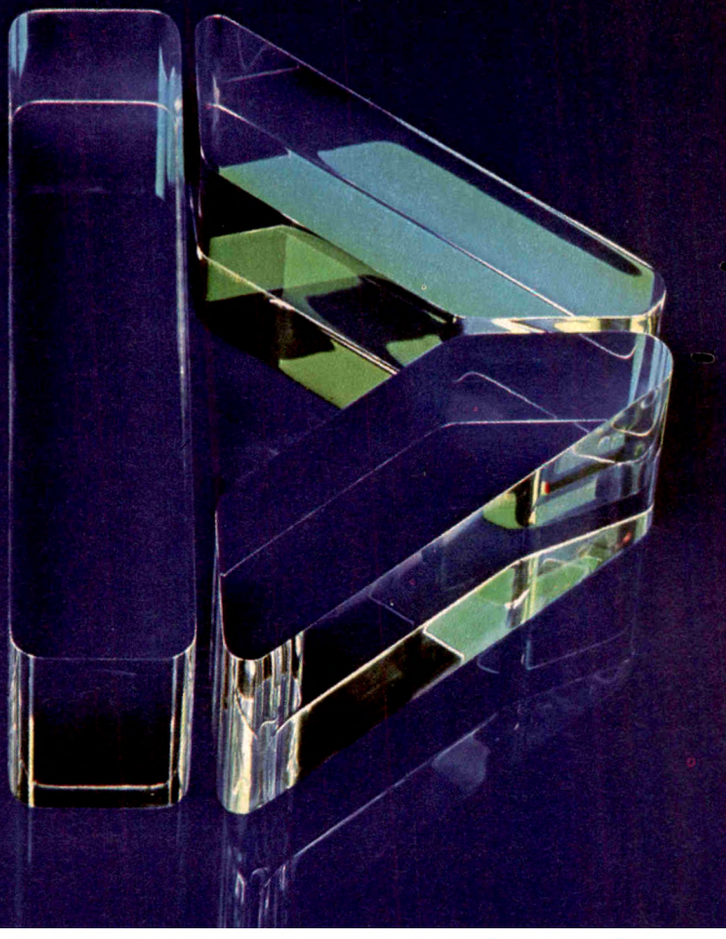

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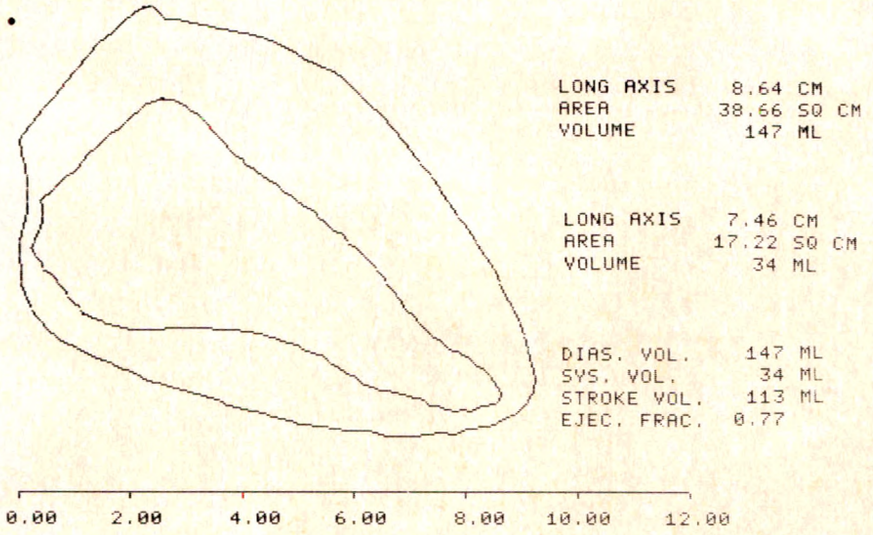

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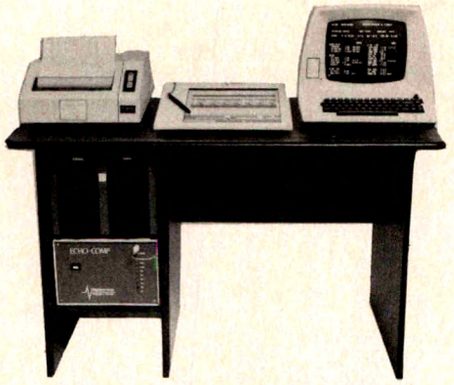

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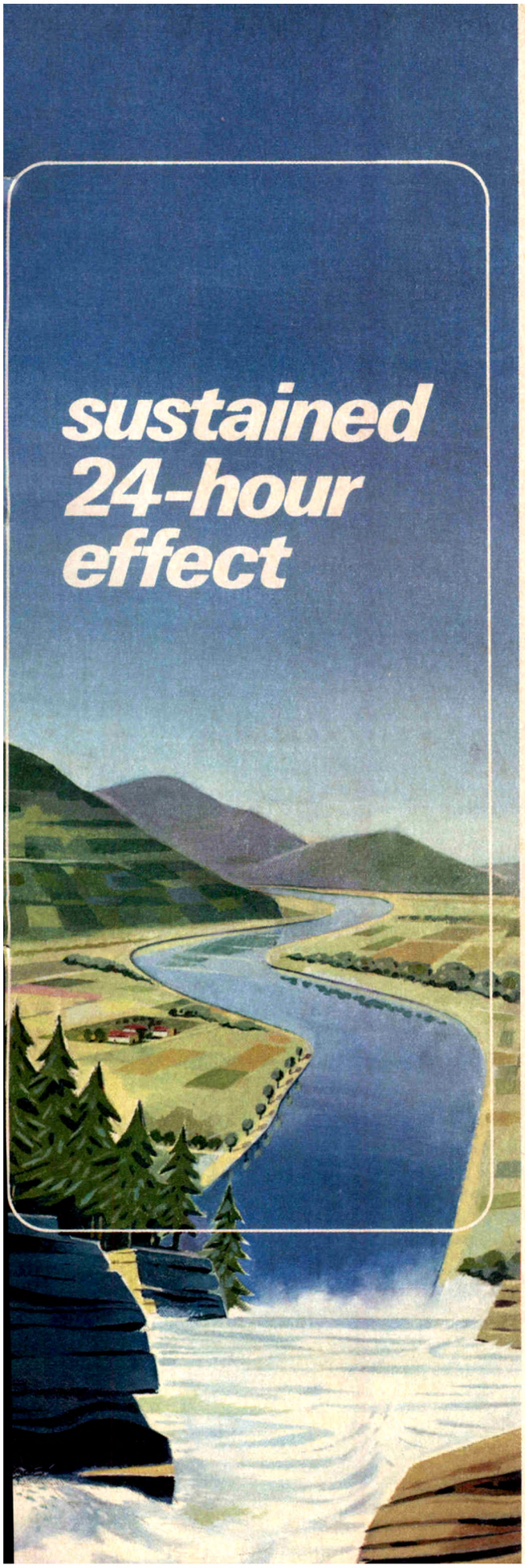

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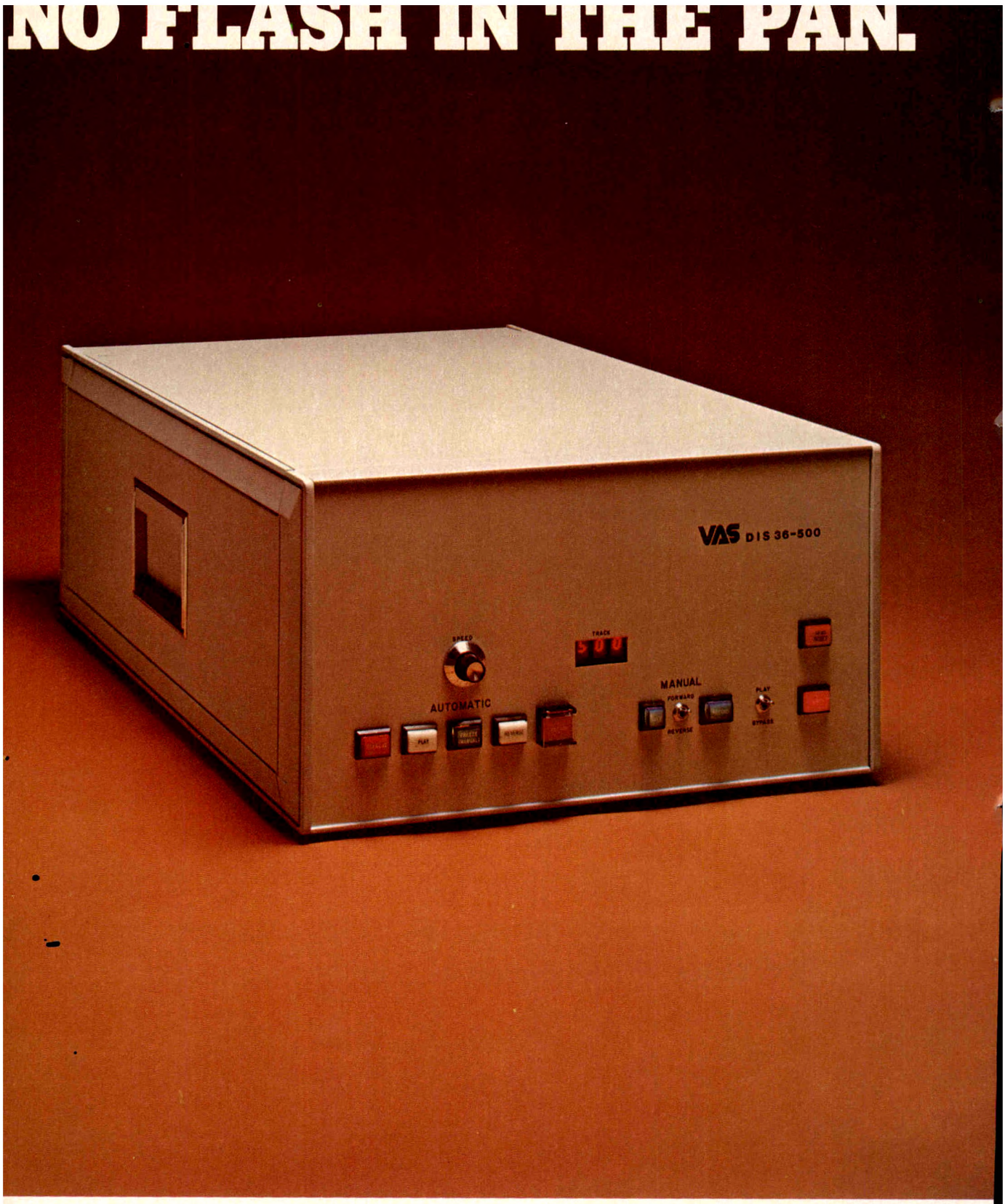

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SUMMARY STATEMENT: **Dennis Krikler, M.D., F.A.C.C.**

Echocardiographic Mimicry of Pericardial Effusion

PATRICIA C. COME, MD*
MARILYN F. RILEY*
NICHOLAS J. FORTUIN, MD†

Boston, Massachusetts
Baltimore, Maryland

Echocardiography is a sensitive technique for the detection of pericardial effusion, but the abnormal echocardiographic patterns seen with effusions are not, however, entirely specific for that diagnosis. This study describes four patients in whom anatomic structures, a coronary artery to coronary sinus fistula (one case) and tumors metastatic to pericardium (three cases), produced posterior and, in two cases, anterior spaces compatible with pericardial fluid. Echocardiographic patterns mimicking pericardial effusion have previously been reported in patients with anatomic abnormalities such as mitral anular calcification, pleural effusions, left atrial enlargement, anterior mediastinal or pericardial tumors, foramen of Morgagni hernia and pseudoaneurysm of the left ventricle. It appears that structures of fluid or tissue density, interposed between the heart and the airfilled lung, can produce echocardiographic patterns simulating pericardial effusion.

Since pericardial effusion was first recognized by ultrasonic techniques in 1955,[1] echocardiography has become the primary means of detecting the presence of pericardial effusion.[2] The technique is sensitive, capable of detecting abnormal patterns of pericardial movement and of epicardial-pericardial separation associated with even minimal effusions.[3] However, the abnormal echocardiographic pattern of a space behind the left ventricular posterior wall or anterior to the right ventricular wall is not entirely specific for the diagnosis of pericardial effusion. Improper technique and intracardiac and extracardiac anatomic abnormalities may produce abnormal echocardiographic patterns that mimic the echocardiographic appearance of pericardial fluid.[2–19]

We describe here four patients in whom anatomic structures located anteriorly and posteriorly relative to the heart produced spaces compatible with pericardial effusion. In the first case, the echocardiographic free space was produced by a large circumflex coronary arterial aneurysm or coronary artery to coronary sinus fistula. In the other three patients, the spaces were produced by metastatic tumors.

Methods

The M mode echocardiographic examinations were performed according to standard technique using a Smith Kline Ekoline 20 A ultrasonoscope, an Irex 101 ultrasonoscope or an Irex System II ultrasonoscope and a 0.5 inch (1.27 cm) diameter, 2.25 megahertz transducer focused at 7.5 cm. The studies were recorded on a Cambridge strip chart recorder, a Honeywell direct writing recorder or an Irex recorder. The two dimensional echocardiographic scans were obtained in several planes using an 80° Varian, model 3000, sector scanner.

Case Reports

Case 1

A 67 year old woman with a history of rheumatic fever at age 17 was admitted to the Beth Israel Hospital to evaluate a 10 to 12 year history of fatigue, exertional dyspnea and epigastric tightness. A murmur had been noted for 50 years. Medications included digoxin and furosemide.

The pulse rate was 72/min and regular and the blood pressure was 125/55 mm Hg. There was no jugular venous distension. Examination of the lungs was normal. There was a right ventricular heave, and a vigorous left ventricular

From the Charles A. Dana Research Institute and the Harvard-Thorndike Laboratory of Beth Israel Hospital, Department of Medicine, Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts* and the Department of Medicine, Cardiovascular Division, The Johns Hopkins University and Johns Hopkins Hospital, Baltimore, Maryland.† Manuscript received August 19, 1980, accepted September 12, 1980.

Address for reprints: Patricia C. Come, MD, Department of Medicine, Cardiovascular Division, Beth Israel Hospital, 330 Brookline Avenue, Boston, Massachusetts 02215.

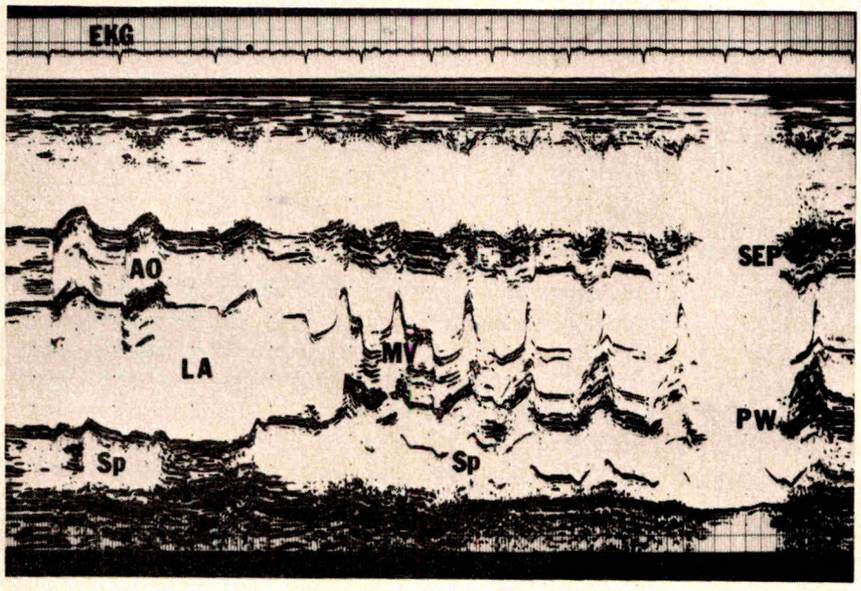

FIGURE 1. Case 1. M mode echocardiographic scan from the aortic root (AO) and left atrium (LA) to the left ventricular apex. Echo-free spaces (Sp) are seen posterior to the left atrium and to the left ventricular posterior wall (PW). EKG = electrocardiogram; MV = mitral valve; SEP = septum.

impulse was palpable in the fifth to sixth intercostal space 2 cm to the left of the mid clavicular line. A grade 2/6 holosystolic murmur was heard at the apex and radiated to the axilla. A continuous murmur was heard over the left lower thorax posteriorly. The electrocardiogram revealed atrial fibrillation and left ventricular hypertrophy and S-T and T wave changes. The chest X-ray film revealed upper zone redistribution and an enlarged heart with apparent right ventricular and left atrial enlargement. No pleural effusion was present.

An echocardiogram (*Fig. 1*) revealed enlargement of the right ventricle and left atrium and a left ventricular diastolic dimension of 5.4 cm. The mitral and aortic valves appeared normal. An echo-free space, measuring in some areas 2 to 2.5 cm, was seen in the area of the atrioventricular (A-V) groove and disappeared with scanning toward the aortic root and left atrium. With damping, all intracardiac echoes disappeared, the only remaining echo being that distal to the space.

At cardiac catheterization, an oxygen content step-up found in the right atrium suggested a left to right shunt. Calculated pulmonary to systemic blood flow ratio was 2.4:1. Aortic root injection (Fig. 2, left) and left coronary angiography revealed a large, long main left coronary artery. There was a very large aneurysm in the proximal left circumflex coronary artery. The remainder of the left circumflex artery was dilated and tortuous and appeared to empty into a dilated coronary sinus. Axial left anterior oblique views obtained following injection of contrast medium into the aortic root and right anterior oblique views obtained during left ventriculography (Fig. 2, right) demonstrated that the descending thoracic aorta was separated from both the left atrium and the left ventricle by the huge coronary arteriovenous fistula and dilated coronary sinus.

At cardiac surgery, there was no evident pericardial effusion. The angiographic findings were confirmed. The distal

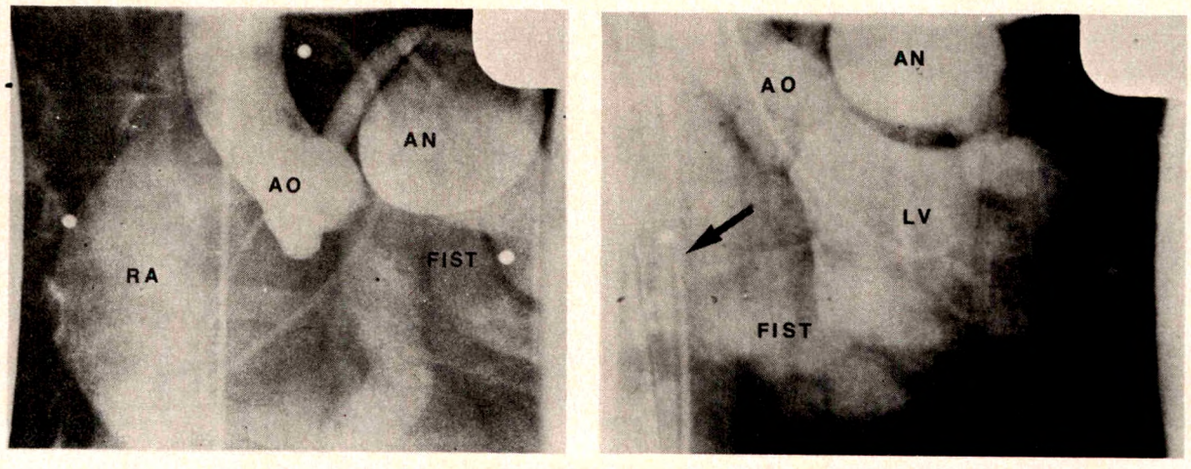

FIGURE 2. Case 1. **Left,** aortic root (AO) injection in the right anterior oblique projection demonstrates a large aneurysm (AN) of the proximal circumflex coronary artery and the coronary artery to coronary sinus fistula (FIST). The right atrium (RA) is seen to fill from the left to right shunt. **Right,** left ventriculogram in the right anterior oblique projection demonstrates the aneurysm (AN) of the left circumflex coronary artery and the large coronary arteriovenous fistula (FIST), which empties into the coronary sinus. The **arrow** points to the location of the angiographic catheter in the descending aorta. The fistula is seen to separate the left ventricle (LV) from the descending thoracic aorta. AO = ascending aorta; LV = left ventricle.

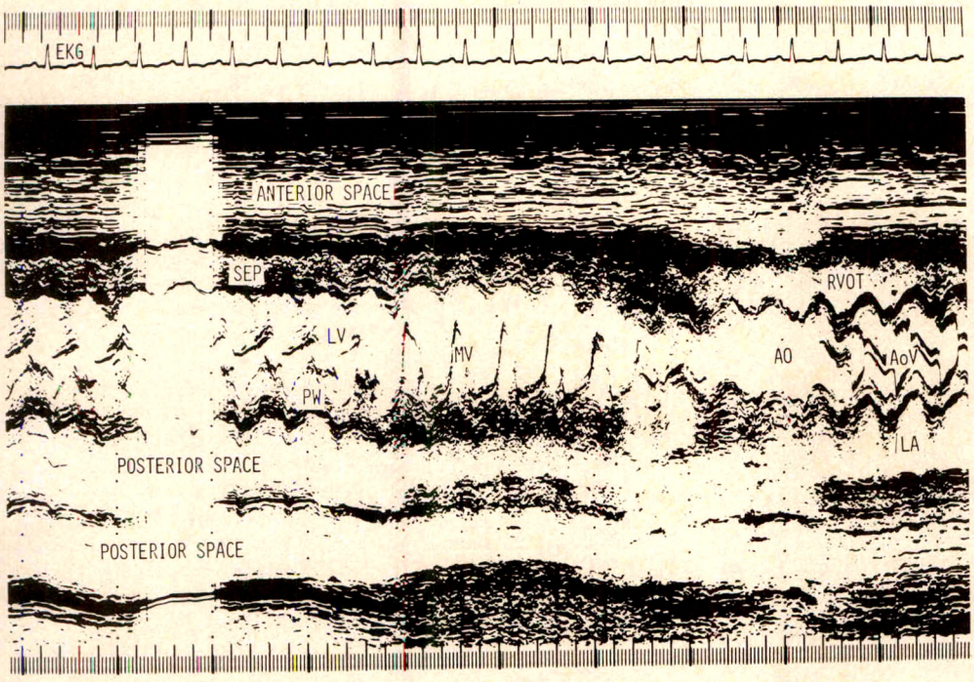

FIGURE 3. Case 2. M mode echocardiographic scan from the left ventricle (LV) to the aortic root (AO) and left atrium (LA). An anterior echo-filled space and two posterior echo-free spaces, all confirmed at autopsy to represent pleural and pericardial infiltration by lymphoma, are visualized. The tumor appeared to compress the right ventricular cavity between the right ventricular wall and septum (SEP). AoV = aortic valve; EKG = electrocardiogram; MV = mitral valve; PW = posterior wall; RVOT = right ventricular outflow tract.

end of the circumflex coronary artery at the site of its anastomosis with the coronary sinus was ligated.

Case 2

A 62 year old man was admitted to the Beth Israel Hospital with increasing dyspnea. After a diagnosis of stage IVB poorly differentiated lymphocytic lymphoma 17 months previously, the patient had received chemotherapy and radiotherapy, including mediastinal and later total body irradiation. Three months before admission, he had undergone chest tube drainage of a left pleural effusion and instillation of tetracycline to sclerose the pleura.

His pulse was 110/min and regular and his blood pressure was 125/60 mm Hg with a 35 mm Hg pulsus paradoxus. His respirations were 27/min and labored. The jugular veins were distended to the angle of the jaw with the patient sitting. Basilar dullness and decreased breath sounds, rales in the mid lung fields and diffuse wheezing were present. The heart sounds were faint and a pericardial friction rub was noted. The liver and peripheral lymph nodes were enlarged. Chest X-ray film revealed hilar lymphadenopathy. The heart appeared enlarged and the epicardial fat pad was seen to lie several centimeters within the anterior heart border on the lateral film. A left pleural effusion was noted on decubitus films and the upper zone pulmonary vessels were distended, suggesting left heart failure.

An echocardiogram was obtained to evaluate the possibility of pericardial tamponade. On M mode echocardiographic study (Fig. 3) an echo-filled anterior space was visualized between the chest wall and the right ventricular wall. Two echo-free spaces were visualized posterior to the left ventricular wall. One appeared to disappear behind the left atrium. There was no swinging movement to the heart. The aortic valve ejection time decreased appreciably during inspiration. Two dimensional echocardiography, including views obtained with long and short axis as well as apical scanning (Fig. 4), demonstrated echo-free spaces surrounding the anterior, apical and posterior parts of the heart. The possibility of a large pericardial effusion could not be excluded, but echocardiographic abnormalities due to pleural effusion and tumor encasement of the heart were considered equally likely. The patient died the following day.

At autopsy, lymphoma was found throughout the body. Lymphomatous infiltration of the pleura on the left resulted in a 1 to 3 cm thick mass in continuity with the mediastinal and hilar lymph nodes. The heart was entirely encased by a 3 to 4 cm thick shell of lymphoma (Fig. 5). Only 150 cc of left pleural fluid and 20 cc of pericardial fluid was found.

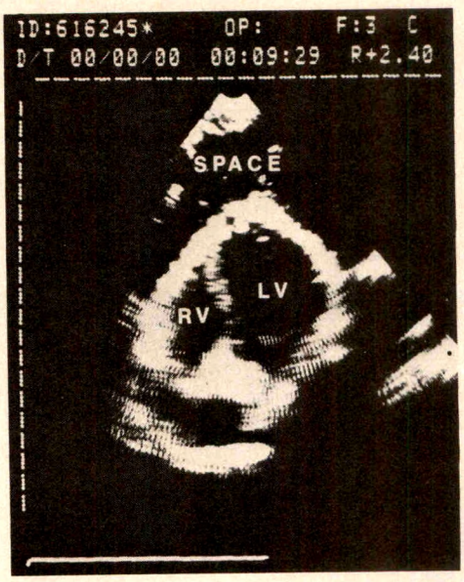

FIGURE 4. Case 2. Two dimensional echocardiogram with the transducer placed at the apex demonstrates a large echo-free space separating the chest wall from the left (LV) and right (RV) ventricular walls. The space appears to surround the base as well as the apex of the heart.

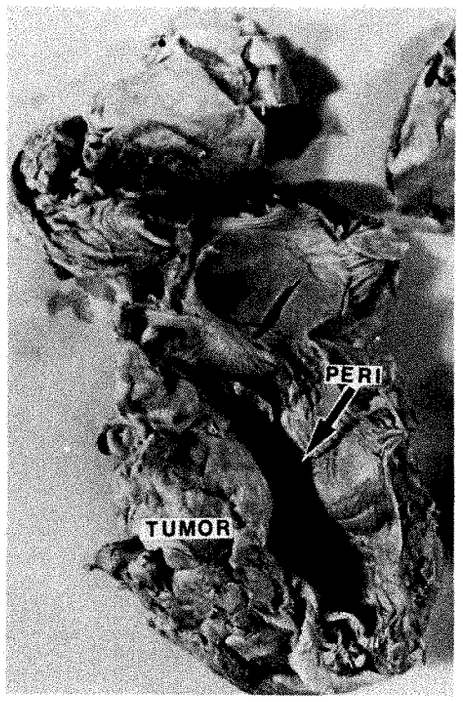

FIGURE 5. Case 2. Autopsy specimen showing the thick tumor surrounding the entire parietal pericardium (**arrow**). The heart has been removed from the pericardial cavity.

Case 3

A 91 year old woman admitted to the Johns Hopkins Hospital for evaluation of lethargy underwent echocardiographic examination to determine the origin of a systolic ejection murmur. The echocardiogram revealed severe thickening and probably calcification of the aortic valve leaflets. However, when best seen, systolic aortic leaflet excursion was maintained, with a maximal cusp separation of 1.6 cm. The pericardial echo was flattened and very minimally separated from the epicardial echo in systole and diastole, suggesting a minimal posterior effusion. With scanning from the apex to the aortic root and left atrium, a 2.3 cm echo-free space was apparent behind the posterior left ventricular wall, in the region of the junction of the left ventricle and left atrium (Fig. 6). The echo-free space disappeared with scanning toward the apex as well as toward the base of the heart. A diagnosis of probable loculated pericardial effusion or pleural effusion was suggested. The patient died unexpectedly.

At autopsy, a squamous cell carcinoma was found to have infiltrated the right middle and right upper lobes of the lung, the diaphragm and the right pulmonary artery. Metastases were found in the lungs, hilar lymph nodes, right and left atria, diaphragm and kidneys. A large, homogeneous-appearing tumor nodule was located on the posterior wall of the heart at the junction of the left ventricle and left atrium.

Case 4

A 65 year old woman who had undergone left pneumonectomy and chemotherapy 1 year previously for oat cell carcinoma metastatic to regional lymph nodes and pleura was admitted to the Beth Israel Hospital with increasing shortness of breath, peripheral edema and ascites. The pulse was 110/min, the blood pressure 110/70 mm Hg and the respiratory rate 30/min. The jugular veins were elevated to the angle of the mandible with the patient sitting. Examination of the lungs revealed basilar dullness and decreased breath sounds. The heart sounds were unremarkable. Ascites and gross peripheral edema were noted. Low voltage was present on the electrocardiogram. A chest X-ray film revealed a moderate-sized right pleural effusion, right lower lobe consolidation and evidence for previous left pneumonectomy.

The echocardiogram was technically difficult to perform, probably because of the mediastinal shift resulting from the prior pneumonectomy. However, definite spaces were detected between the chest wall and the right ventricular wall and between the posterior left ventricular wall and the presumed posterior pericardium (Fig. 7). The differential diagnosis was considered to include both pericardial effusion and tumor metastasis to the pericardium.

The patient had progressively increasing shortness of breath, tachycardia and hypotension. She was judged not to be a candidate for further chemotherapy and died.

Autopsy revealed oat cell carcinoma involving the entire left thoracic cavity. One to two cm thick tumor encased the heart. Seventy-five cc of fluid was present within the pericardial cavity.

Discussion

The pericardial space separating the epicardium and the parietal pericardium normally contains only a very

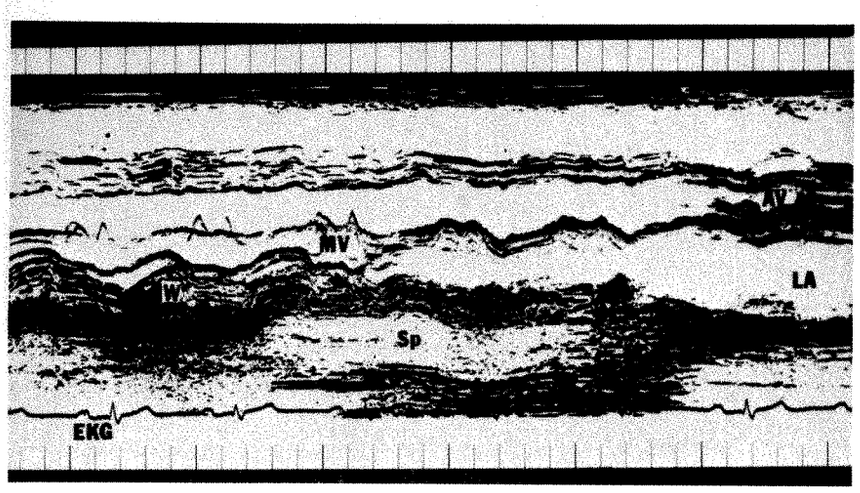

FIGURE 6. Case 3. M mode echocardiographic scan from the left ventricle to the aortic root and left atrium (LA). An echo-free space (Sp) is seen below the posterior left ventricular wall (W), near its junction with the left atrium. AV = aortic valve; EKG = electrocardiogram; MV = mitral valve.

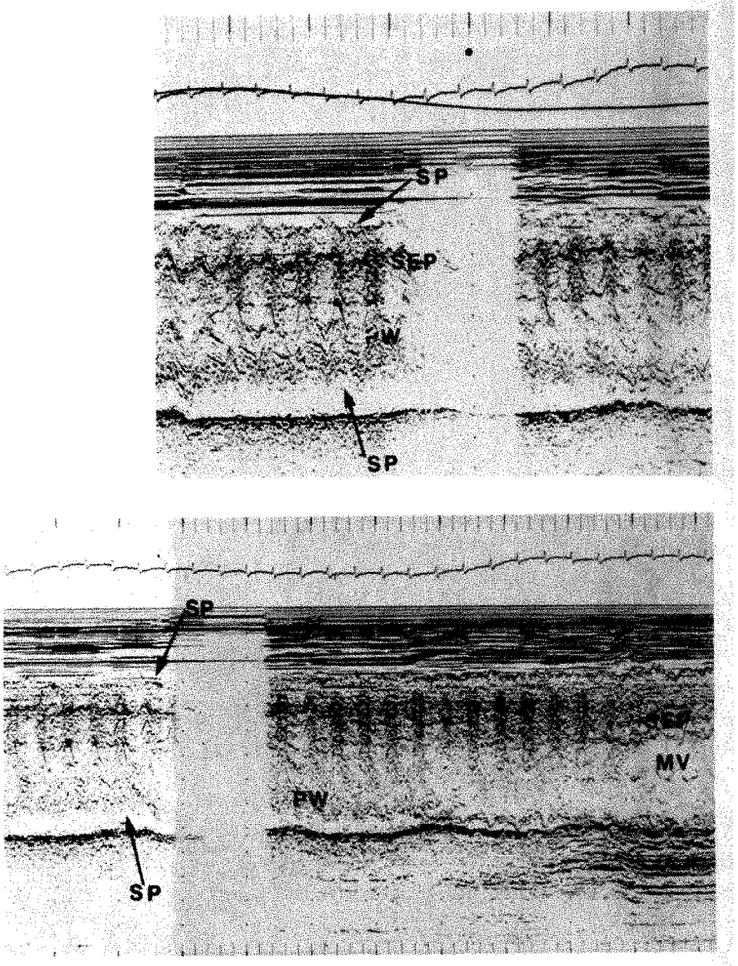

FIGURE 7. Case 4. **Top,** the left ventricular echogram was technically difficult to obtain in this patient because of her prior pneumonectomy. However, in the left ventricular area an anterior echo-free space (SP) and a posterior space (SP), measuring up to 2.3 cm, were visualized, suggesting a sizable pericardial effusion. The most intense distal echo, which could easily be mistaken for pericardium, was nonmoving. **Bottom,** M mode echocardiographic scan from the left ventricle to the mitral valve (MV) again demonstrates anterior and posterior spaces (SP) easily mistaken for a moderately large pericardial effusion. The heater element in the recorder has caused the differences in paper color. PW = posterior wall; SEP = septum.

small amount of fluid.[2,20–22] Echocardiographically, the pericardium can normally be recognized as the structure immediately adjacent to and moving in concert with the outer surface of the ventricular wall.[2,3] It is normally the strongest reflector of ultrasound in the heart because it serves as a specular reflector and because it separates heart muscle from the air-filled lung, which has an acoustic impedance only a fraction of that of other body tissues,[23] including the heart. Therefore, when the amount of energy emanating from the echocardiographic transducer is decreased, with use of a technique known as damping, the posterior pericardial echo is usually identified as the last remaining echo.

Echocardiographic signs of pericardial effusion: A pericardial effusion represents accumulation of excess fluid between the epicardium and pericardium. Because the pericardium remains a specular reflector and continues to separate the air-filled lung from a medium, now fluid, with a higher acoustic impedance, it will still be identifiable echocardiographically as the strongest reflecting surface. However, a space, usually echo-free but occasionally echo-filled, will now be seen between pericardium and epicardium.[2,3] This space typically disappears behind the left atrium because of the tight reflection there of the pericardium onto the pulmonary veins.[2,9,20–22] Occasionally, in the case of a large effusion or one under increased pressure, pericardial fluid may be seen behind the left atrium.[2,8,9] If an effusion is very small, the pericardial echo may retain some movement.[3] However, as the size of the effusion increases, the pericardium becomes insulated from the movement of the epicardium, causing the pericardial echo to become nonmoving,[2,3] and an anterior echo-free space may develop.

Simulators of pericardial effusion: In the four patients presented, spaces were visualized echocardiographically between the left ventricular epicardium and the strongest reflecting surface distal to the heart, suggesting pericardial effusions. However, no effusion was detected at surgery in the first patient and only 20, 36 and 75 cc, respectively, of pericardial fluid was found at autopsy in the others. The large echo-free spaces seen on ultrasonic examination were almost certainly produced by the large coronary artery to coronary sinus fistula or coronary aneurysm in Case 1 and by the pericardial metastases in the other three cases. The posterior margins of the fistula and of the tumors were likely the most intense echo-producing interfaces because, lying posterior to the cardiac wall, they separated the air-filled lung from soft tissue. The echo-free space in Case 3 simulated a loculated pericardial effusion because it was limited to the level of the tumor and the pericardium appeared normal above and below this level. Occasionally the posterior thoracic aorta may be

visualized as an echo-free space posterior to the heart. This possible cause of the echo-free space was excluded in Patient 1 by cineangiography (Fig. 2B). Lymphoma and carcinoma separated the heart from the descending thoracic aorta in Patients 2 and 4. Visualization of the aorta posterior to the A-V groove cannot be definitely excluded as the reason for the posterior echo-free space in the third patient. However, the discovery of a large metastatic carcinoma nodule in an anatomic position corresponding to the echo-free space seen on ultrasonic examination strongly suggests that the echo-free space was, in fact, produced by the tumor nodule. It should be noted that tumor encasement of the heart, as in our Case 2, may result in clinical and echocardiographic findings that resemble those observed in pericardial tamponade.

Other conditions mimicking pericardial effusion: Other unusual pathologic conditions previously reported to produce echocardiographic patterns compatible with pericardial effusion include a markedly dilated left atrium,[10] a foramen of Morgagni hernia,[11] a large retrosternal lymphoma,[2] left ventricular pseudoaneurysms[12–15] and a tumor involving the pericardium that resulted in an echo-filled space between the left ventricular posterior wall and the distal pericardial echo.[24] Mitral anular calcification[6,7] and pleural effusions[8,9] have been recognized as more common anatomic abnormalities capable of producing echocardiographic patterns that could be misinterpreted as representing pericardial effusions. In addition, it is recognized that normal anatomic structures such as the left inferior pulmonary vein,[16] the descending thoracic aorta and the coronary sinus,[17–19] especially when dilated, may produce echo-free spaces posterior to the heart.

Differential diagnosis: Echocardiography is a sensitive technique for the identification of pericardial fluid[3] and has become the foremost tool for evaluating patients with suspected effusion. Because an improper diagnosis of pericardial effusion may result in unwarranted pericardiocentesis or more aggressive surgical procedures, appropriate attention must be paid to recognition of technical artifacts and to consideration of other anatomic conditions that may simulate pericardial effusion. Slow scanning from the apex to the base of the heart will allow visualization of the location of the echo-free space relative to the left ventricular and left atrial walls and allow assessment of left atrial wall movement. Such scanning may permit differentiation of pericardial fluid from other common anatomic abnormalities such as pleural effusion and mitral anular calcification. The presence of a somewhat atypical echocardiographic pattern of pericardial effusion, such as apparent loculation of fluid or the absence of an anterior echo-free space in a patient with an apparent large posterior pericardial effusion, should raise the possibility of a false positive diagnosis. Such a diagnosis might be caused by the presence of a vascular structure or solid mass adjacent to the posterior left ventricular wall. Two dimensional echocardiography, which permits visualization of anatomic structures in two distance dimensions, is becoming increasingly available and may also facilitate differential diagnosis.

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"Supernormal" Phase of Atrioventricular Conduction With Concealed Capture Beats

Significance of Odd Numbers of P Waves Between Capture Beats

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In 1968 Moe and associates postulated multilevel atrioventricular (A-V) block as a mechanism for some forms of the supernormal phase of A-V conduction. In 1971 Schamroth further postulated that, if this were correct, there would only be odd numbers of sinus P waves between the capturing impulses. This report presents two cases of sinus rhythm dissociated from idionodal escape rhythm as a result of high grade A-V block. The rhythm is complicated by manifest and concealed A-V captures during the so-called supernormal phase. There are only odd numbers of P waves between the capturing impulses.

The "supernormal" phase of atrioventricular (A-V) conduction is an apparent paradoxical electrocardiographic manifestation wherein relatively early supraventricular impulses, which should encounter more refractoriness, are conducted through the A-V node to the ventricles, and where relatively late supraventricular impulses, which should encounter less refractoriness, are blocked. Many of these so-called paradoxical manifestations of the "supernormal" phase of A-V conduction have been examined in elegant studies[1] and are subject to logical electrocardiographic deduction. The following two cases are of special interest because they reflect, for the first time, concealed supernormal A-V nodal penetration and also provide confirmatory evidence of a mathematical hypothesis that was propounded to explain this particular manifestation of A-V nodal supernormality.[2]

Case Reports

Case 1

The electrocardiogram (Fig. 1, a continuous strip of lead V_1, and Fig. 2, a later strip of the same lead, diagrammed) was recorded from an elderly man with a 1 week history of weakness. He was taking no medications.

The electrocardiogram in Figure 1 shows a basic normal sinus rhythm. The P-P intervals measure 0.84 second, representing a sinus rate of 71/min. Most of these sinus P waves are dissociated from an A-V junctional escape rhythm with an R-R interval of 1.52 seconds, representing a heart rate of 39 beats/min. This basic manifestation is reflected by the first two QRS complexes and the first four P waves in the top strip. This dissociation between a faster sinus rhythm and a slower A-V nodal escape rhythm represents high degree A-V block. Some of the ensuing sinus impulses that occur very early in the R-R interval and others that are so early that they actually precede the R wave (of the R-R interval containing the capture [see later]) and thus occur very late in the preceding R-R interval are conducted.

Conduction may take one of the following forms: (a) through the A-V node without reaching the ventricles; (b) through the A-V node and with normal intraventricular conduction; and (c) through the A-V node and with aberrant ventricular conduction resulting in a left or a right bundle branch block pattern. These sinus impulses are labeled with numbered arrowheads in Figure 1. Impulses 3 and 5 are conducted normally to the ventricles resulting in capture beats

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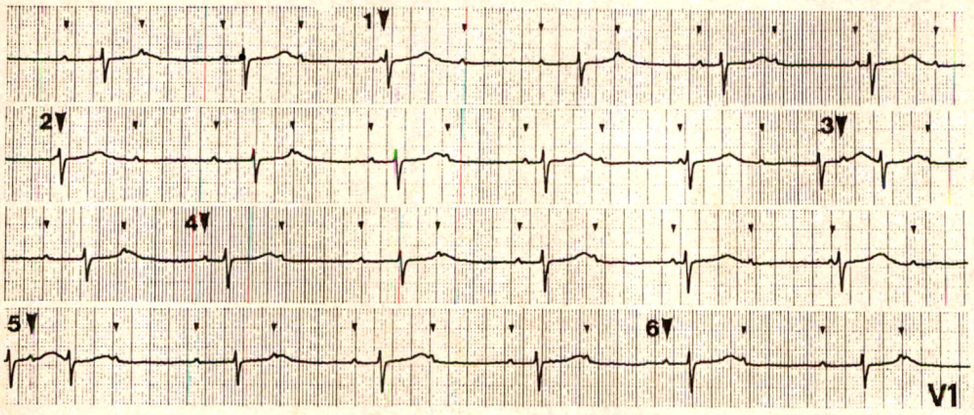

FIGURE 1. Case 1. Electrocardiogram (a continuous strip of lead V_1) showing manifest and concealed 'supernormal' captures with only odd numbers of intervening P waves. **Arrows** reflect the capturing impulses.

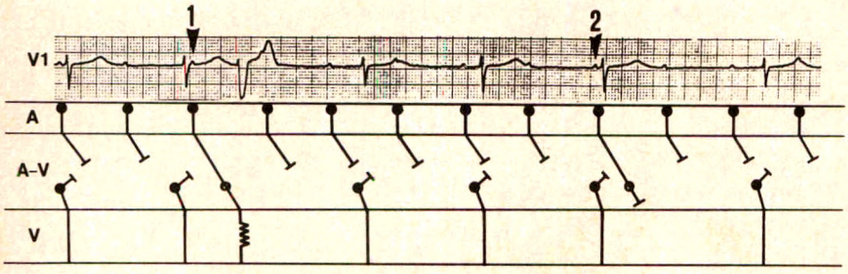

FIGURE 2. Case 1. A later diagrammed section of lead V_1. **Arrows** reflect the capturing impulses.

with a normal QRS complex (form b). The first capturing impulse in Figure 2 is conducted with a left bundle branch block pattern (form c). Other capturing impulses (1, 2, 4, 6 in Fig. 1 and the second capturing impulse in Fig. 2) reflect concealed A-V nodal conduction (form a). This is evidenced by the resetting of the A-V nodal cycle due to the premature discharge of the A-V nodal pacemaker by the concealed A-V nodal penetration of the supraventricular impulse. The postponed A-V nodal cycle results in a relatively long R-R interval. These intervals range from 1.82 to 2.08 seconds.

The relation to the near synchronous QRS complex of the sinus impulses resulting in concealed conduction, aberrant ventricular conduction and normal intraventricular conduction is depicted in Figure 3. P waves that occur relatively late after the R wave are associated with normal intraventricular conduction (open circles in Fig. 3). P waves that occur relatively early after the R waves are associated with right or left bundle branch block (cross in Fig. 3). P waves that occur synchronously with or before the R wave are associated with concealed conduction (black dots in Fig. 3). There were three instances of concealed conduction with P waves that overlapped with, or occurred later than, the period of bundle branch block conduction. These probably reflect a critical state of bundle branch refractoriness. It is also noteworthy that a sinus impulse that occurs 280 ms before the QRS complex can capture the A-V nodal pacemaker after the manifest discharge, as represented by the QRS complex, and reset the ensuing A-V nodal cycle. This reflects an exceptionally long partial refractory period in the upper part of the A-V node.

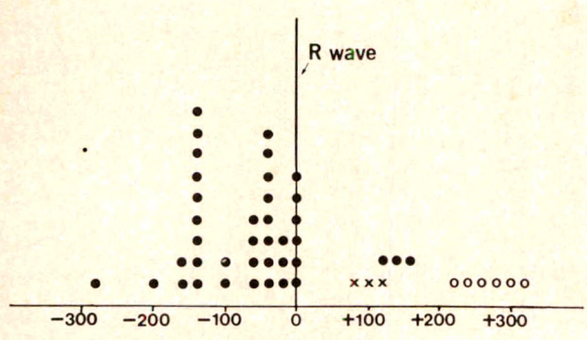

FIGURE 3. Case 1. Diagram illustrating the P to R or R to P relationship of capturing sinus impulses. The **closed circles** or **dots** represent concealed conduction. The **crosses** represent conduction with bundle branch block. The **open circles** represent capture with normal intraventricular conduction. Figures represent milliseconds.

The P waves between the sinus impulses that penetrate into the A-V node or are conducted to the ventricles occur in odd numbers only. Thus, between the various arrows in Figure 1 are seven, nine, three, nine and seven P waves, respectively; and there are five P waves between the capturing impulses in Figure 2. Forty-seven intervals between capture beats were observed and, with one exception, the P waves in these intervals occurred in odd numbers. The exception was an interval with two intervening sinus P waves.

Case 2

The electrocardiogram (Fig. 4, a continuous strip of lead V_1) was recorded from a 77 year old man who went into a coma 2 days before the insertion of a pacemaker; the tracing was recorded at a later date when the pacemaker failed. The small ineffective pacing spike artifacts are evident throughout the tracing. The P-P intervals of the basic sinus rhythm measure 0.79 second, representing a heart rate of 76 beats/min. The sinus rhythm is dissociated from an A-V junctional escape rhythm as represented by the narrow and normal QRS complexes. The R-R intervals measure 1.42 seconds, representing

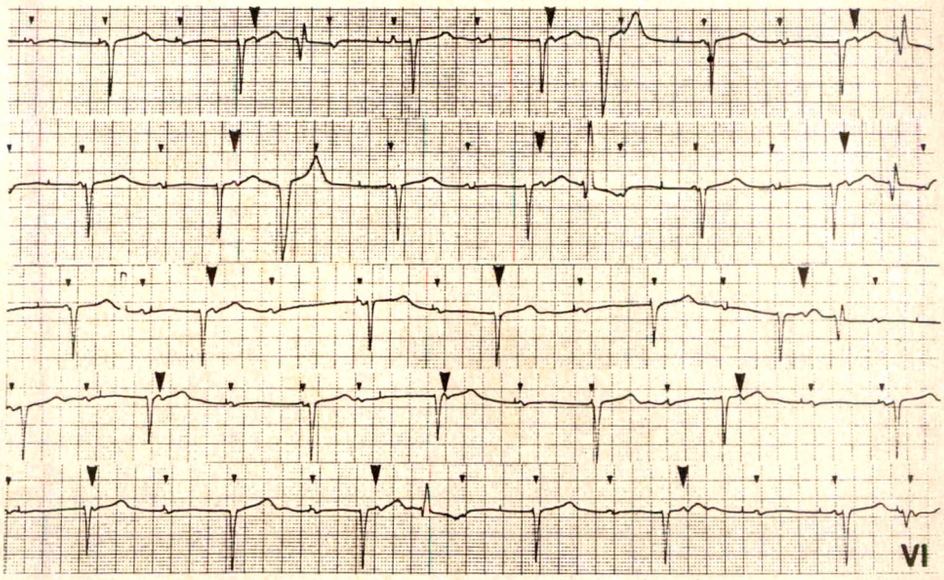

FIGURE 4. Case 2. Electrocardiogram (a continuous strip of lead V_1) showing manifest and concealed 'supernormal' captures with only odd numbers of intervening P waves. **Arrows** reflect the capturing impulses.

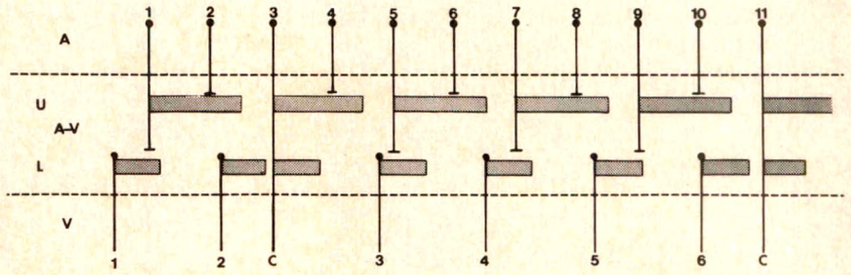

FIGURE 5. Diagram illustrating the effect of differential horizontal A-V junctional refractoriness. There is 2:1 A-V block in the upper part of the A-V node (U) with 1:1 conduction in the lower part of the A-V node (L).

a heart rate of 42 beats/min. This dissociation between a faster sinus rhythm and a slower A-V junctional escape rhythm reflects the presence of high grade A-V block. Sinus impulses that occur very early in the cycle (labeled with a large arrowhead) are conducted. These represent the "supernormal" phase of A-V conduction because later impulses are blocked.

The conduction takes one of the following forms: (1) Conduction to the ventricles with right bundle branch block. This pattern is represented by the first and last captures in the top strip (Fig. 4). (2) Conduction to the ventricles with left bundle branch block. This pattern is represented by the second capture beat in the top strip and the first capture beat in the second strip. (3) Concealed A-V nodal conduction. This pattern is reflected by resetting of the A-V nodal cycle by the sinus impulse that penetrates into the A-V node to discharge the A-V junctional pacemaker but fails to reach the ventricle. It is represented by the long cycles in the third and bottom strips, which reflect concealed supernormal capture beats.

The sinus impulses intervening between the capture beats (labeled with the small arrowheads) occurred, as in Case 1, in odd numbers only. Seventy-six such intervals were analyzed and these contained only odd numbers of P waves (Table I).

Discussion

Mechanisms of supernormal phase of A-V conduction: Several hypotheses have been put forward to explain the supernormal phase of A-V conduction. For example, phase 4 A-V block may explain the block of late impulses and the conduction of relatively early impulses. Another possible mechanism (based on the work of Moe et al.[1]) is the assumption of differential "horizontal" refractoriness within the A-V node (Fig. 5). The refractory period of the upper part of the A-V node (U) is longer than the refractory period of the lower part of the A-V node (L). This results in a 2:1 A-V block in the upper part of the node, and 1:1 conduction in the lower part. The 2:1 A-V block increases the effective sinus cycle at the level of the lower A-V node; that is, the conducted sinus cycle at this level is, in effect, twice the normal sinus cycle. This is represented, for example, by the interval between sinus impulses 1 and 3. This in-

TABLE I

Case 2. Analysis of Numbers of P Waves Between the Capture Impulses

P Waves (n)	Measurements (n)
1	3
3	61
5	10
7	2
Total	76

crease in the effective conducted sinus cycle permits the escape of a subsidiary A-V nodal pacemaker situated in the lower part of the A-V node.

Although the A-V junctional cycle (represented by A-V nodal impulses 1 and 2, Fig. 5) is longer than the true sinus cycle, it is shorter than the effective conducted sinus cycle. The A-V nodal rhythm thus escapes through default of the sinus impulse as a result of the 2:1 A-V block. Interference dissociation now ensues between (1) the sinus impulses represented by the effective conducted sinus cycle, and (2) the A-V nodal impulses. The A-V dissociation is complicated by occasional ventricular capture beats (labeled C) (the momentary conduction of the sinus impulse to, and capture of, the ventricles). This creates the illusion of a paradoxical situation. The P wave representing the conducted impulse occurs at a relatively short R-P interval after the preceding A-V junctional beat—represented by the interval between A-V nodal beat 2 and the ensuing capture beat (interval 2-C). Interval 6-C is an analogous situation. P waves that occur at longer R-P intervals are "paradoxically" not conducted; for example, sinus impulse 8 occurs at a long R-P interval after A-V nodal impulse 4 and yet is blocked. The capture beats are thus conducted in an early critical phase of the lower cycle.

Hypothesis of only odd numbers of intervening P waves: When this particular form of interference dissociation occurs, namely, 2:1 A-V block in the upper A-V node associated with 1:1 conduction in the lower A-V node, only odd numbers of P waves can occur between the intervening capture beats. This is because only the odd-numbered impulses can penetrate the upper part of the A-V node. Their conduction through the lower part of the A-V node will depend on the state of responsiveness resulting from the A-V junctional escape rhythm. For example, in Figure 3 there are only seven P waves (numbered 4 to 10) between the two capture beats.

This theoretical mathematical manifestation of the hypothesis of Moe et al.[1] was first propounded by Schamroth[2] in 1971, and there can be no doubt from the many observations in these two cases that the hypothesis of only odd numbers of intervening P waves holds. This mathematical manifestation thus confirms the original hypothesis proposed by Moe et al.[1] in 1968. This case is thus of particular interest because the phenomenon of concealed supernormal A-V captures has not previously been described, and the mathematical hypothesis of the intervening odd numbers of sinus beats to confirm the hypothesis of differential horizontal refractoriness is now clearly established.

Acknowledgment

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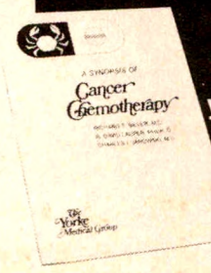

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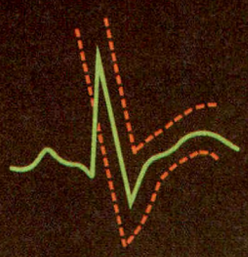
No other arrhythmia detection system gives you all three.

1



2

Dramatically reduced false alarms

We start with template matching—the preferred method—to discriminate between the patient's dominant beat and ectopics. But only Arrhythmia II adds two unique features to screen out artifact, ensuring that only qualified ectopic activity triggers alarms or is included in trends: (1) each abnormal beat must appear four times before it's accepted as a "true" ectopic class, and (2) our "over-range" circuitry suspends ECG processing for a minimum of five seconds when it detects excessive noise.

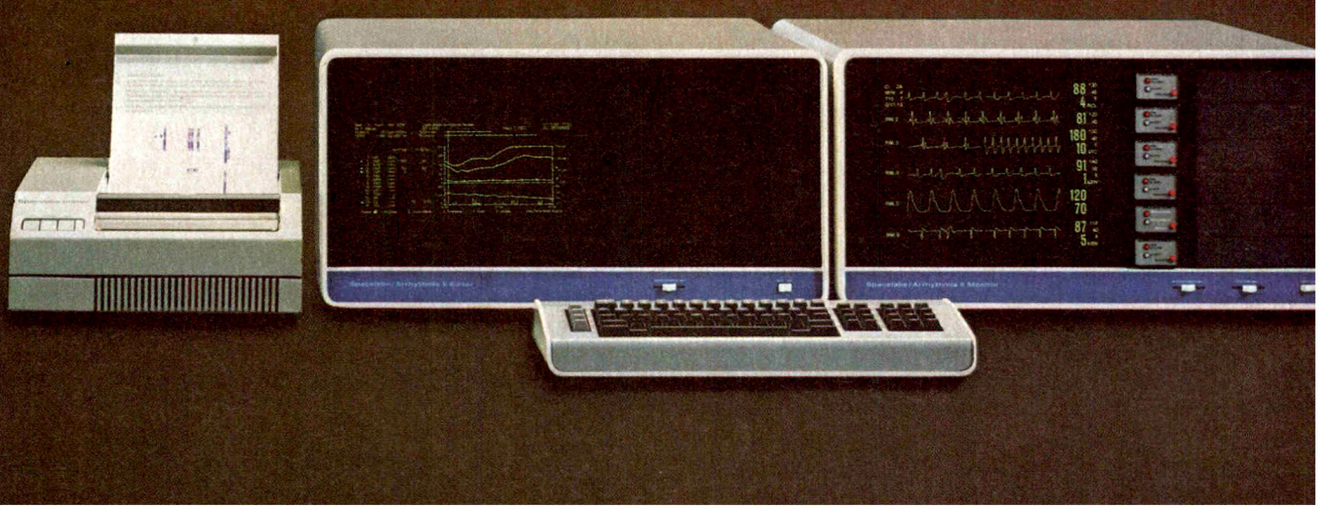
MEMORY BANK OF CLASSES		NUMBER OF OCCURRENCES 1	2	3	4	5	6	7 →
C-0	NORMAL	*	*	*	*	*	*	* *
C-1		•	•	•	•	*	*	
C-2		•	•					
C-3		•						
C-4		•	•	•	•	*		
C-5		•						
C-6								
C-7								
C-8								
C-9								
C-10								
C-11								
C-12								
C-13	COUPLET							
C-14	DROPPED BEAT							
C-15	PACED							

4-MATCH CRITERIA

More meaningful patient information

Other computerized arrhythmia detection systems may accurately detect and record ectopic activity. But we just start there. Only Arrhythmia II allows you to select those ectopics that are particularly important for a patient and to include only those ectopics in trends. You can quickly recall classes of ectopics and their frequency over 24 hours. And, on the Editor, you can trend a specific class or combination of classes for 1, 2, 8 or 24 hours, without having to edit out each occurrence of unwanted information.

Arrhythmia II



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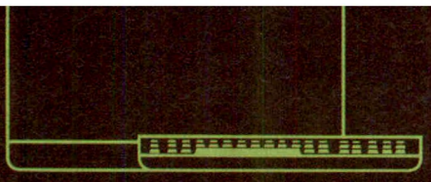

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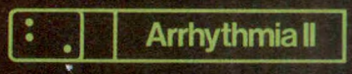
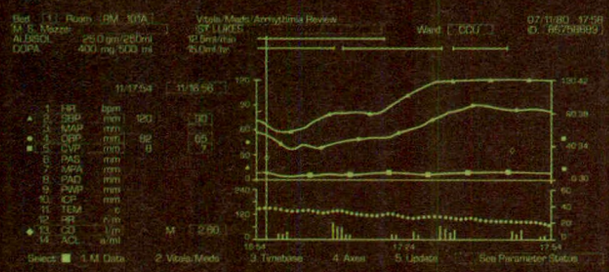


See effects of treatment on one screen

Only Arrhythmia II lets you trend medications, ectopics and vital signs on one display, in a concise and easy-to-interpret format. And it provides 24-hour recall so the precise information on ectopics, vital signs and medications is available for any specific time.



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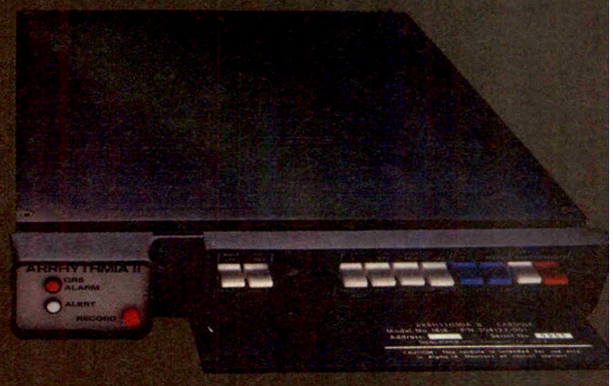
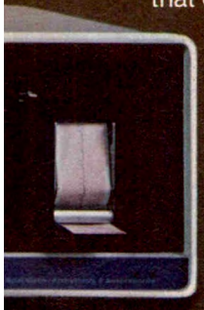
Hospitals using minicomputer systems have experienced the loss of critical data on all patients connected to the system when the computer malfunctions. But that can't happen with Arrhythmia II, because each patient has his own computer. And any malfunction only affects that one patient. The microprocessor-based cardule can then be replaced in minutes and easily repaired by simply inserting a new circuit board.



We designed Arrhythmia II to solve clinical problems that other arrhythmia systems have not even tried to solve. We feel it represents our care and concern in applying technology to the clinical setting—an approach that has made Spacelabs the fastest growing company in patient monitoring today.



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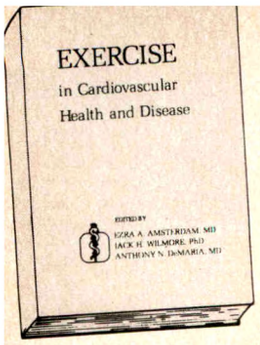

For **every** professional with an interest in Exercise and the Heart.

EXERCISE in Cardiovascular Health and Disease

Edited by
Ezra A. Amsterdam, MD, Chief Coronary Care Unit, Univ. of Calif. School of Medicine
Jack H. Wilmore, PhD, Professor and Head Dept. of Physical Education & Athletics, Univ. Arizona
Anthony N. DeMaria, MD, Dir. Echocardiography Section, Univ. of Calif. School of Medicine

SEPTEMBER 1977, 408 PAGES, ILLUS.

This comprehensive work covers every aspect of exercise and its role in Diagnosis, Treatment, and Prevention of cardiac disease.

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- ☐ Computer analysis of the exercise ECG
- ☐ Stress myocardial scintigraphy
- ☐ Various interpretations of exercise tests in the asymptomatic population

The editors have brought together a distinguished group of specialists—all of whom have made major contributions to the field. Included are outstanding scientists, clinicians, exercise physiologists, and physical educators.

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SLOW-RELEASE TABLETS 10 mEq

DESCRIPTION KLOTRIX is a film-coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS— BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).
Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.
All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.
Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.
Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.
Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE Usual dietary intake potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.
Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.
Note: KLOTRIX slow-release tablets must be swallowed whole and never crushed or chewed.
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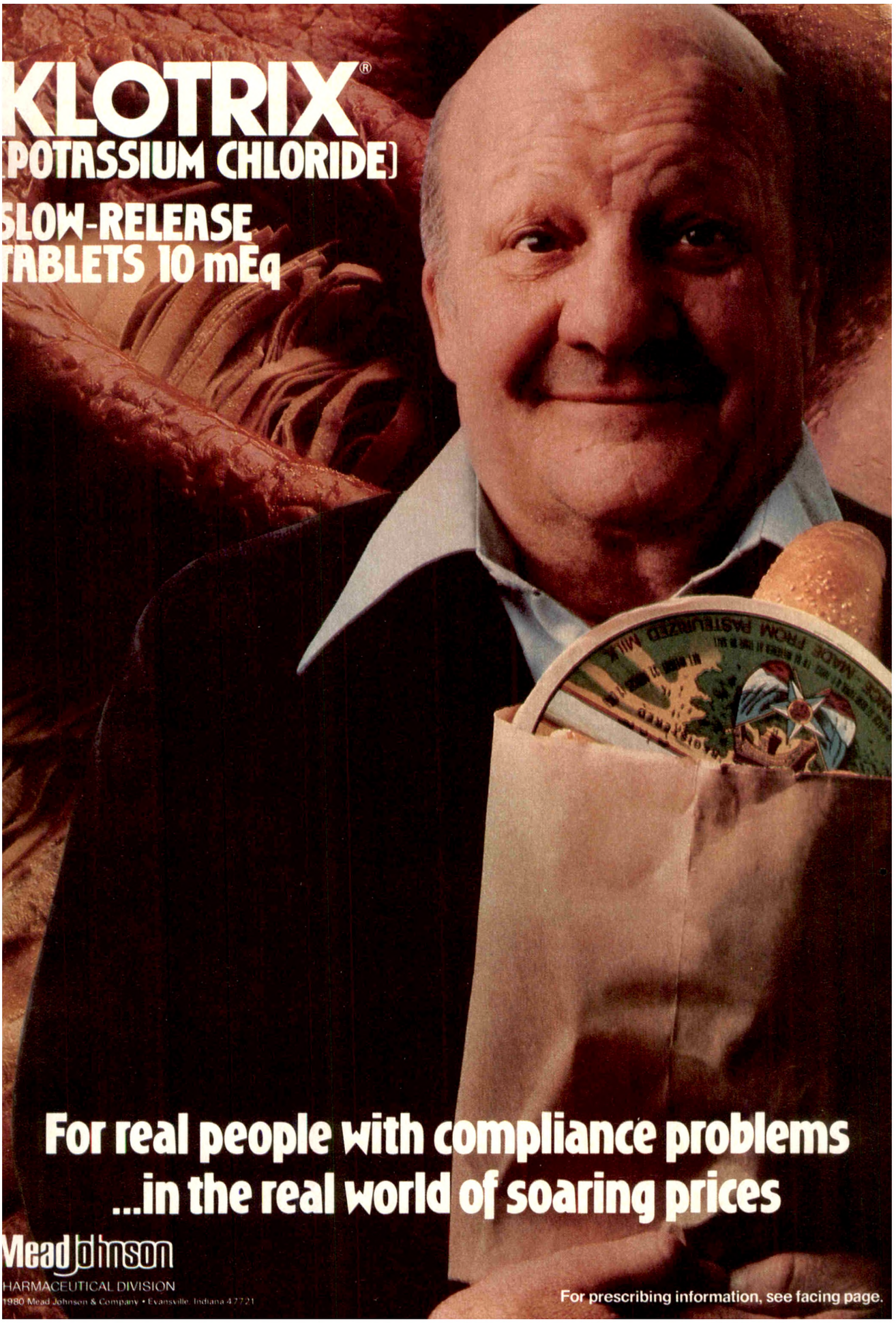
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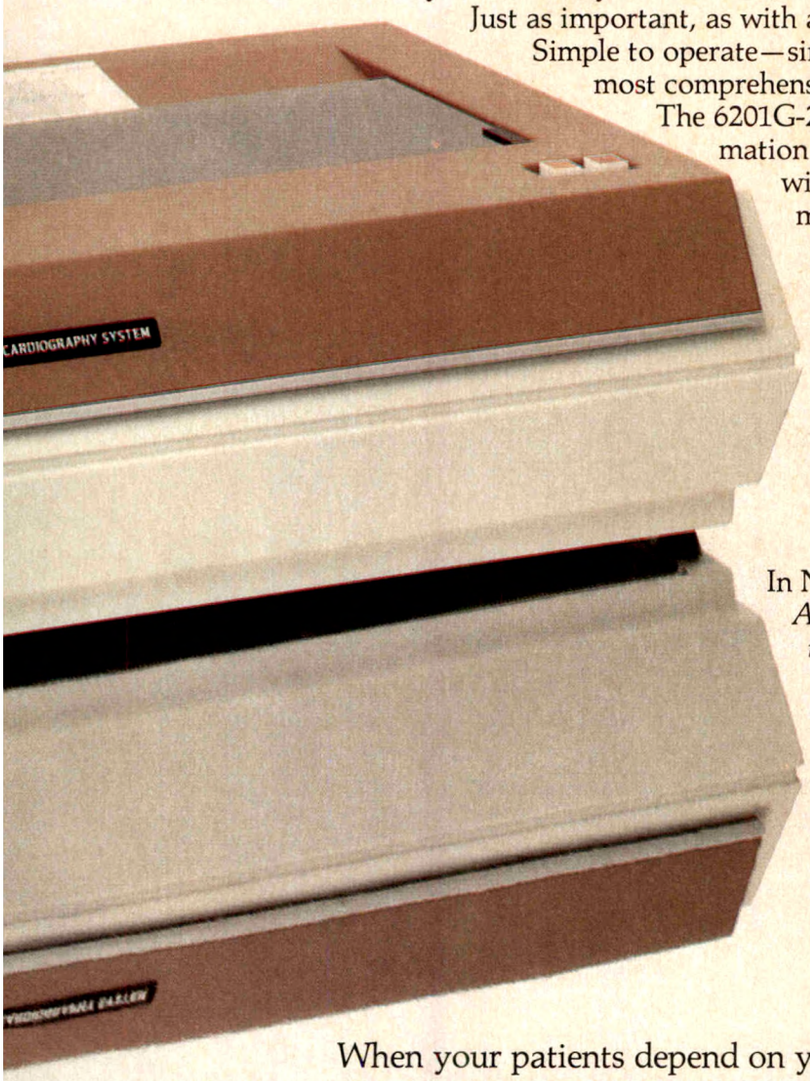

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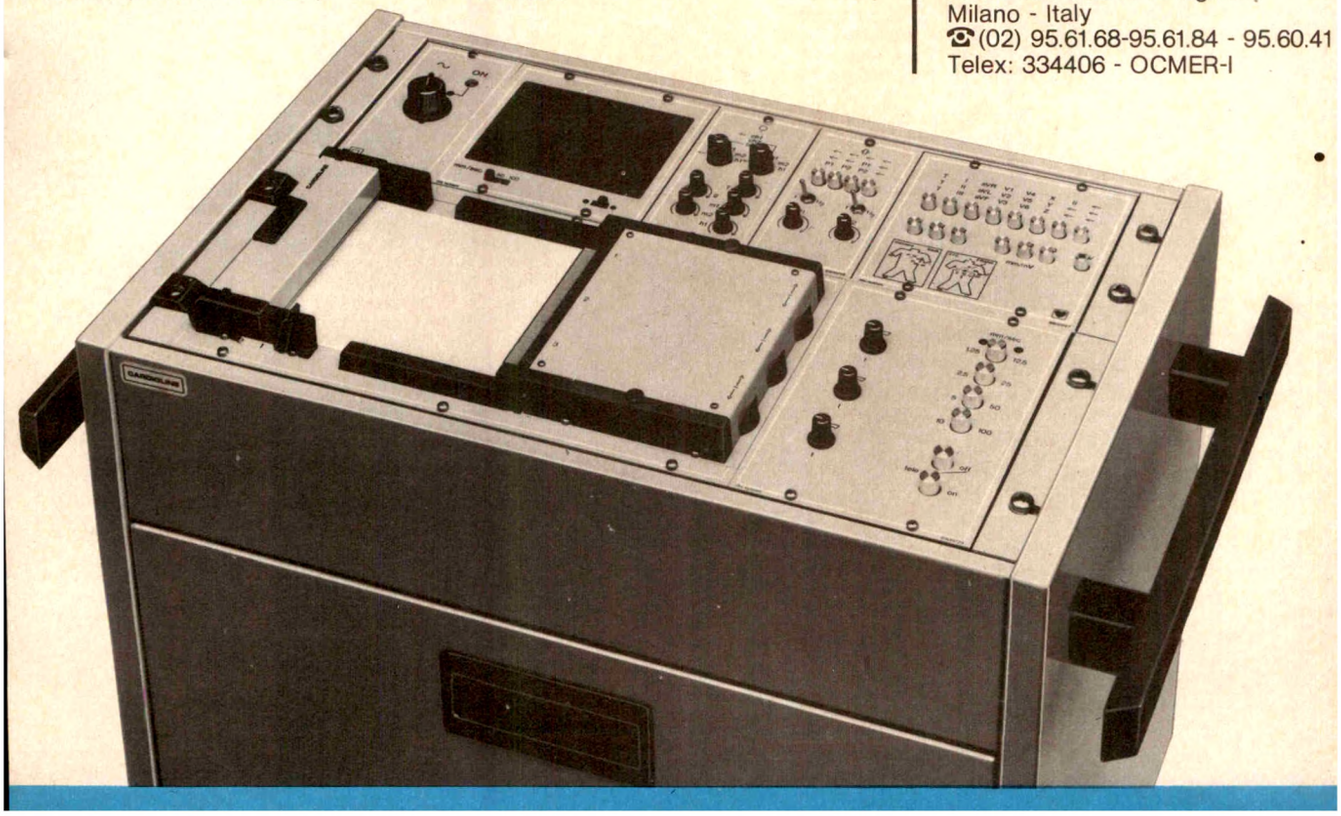

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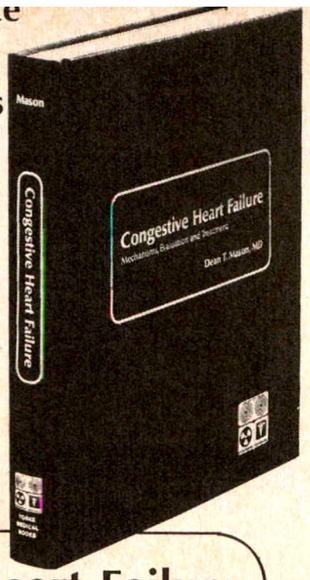

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About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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Aldactone®
(spironolactone)

WARNING
Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see Warnings). Aldactone should be used only in those conditions described under Indications. Unnecessary use of this drug should be avoided.

Indications: *Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.*

Contraindications: *Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.*

Warnings: *Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics.*

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: *Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced.*

Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.

Adverse Reactions: *Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.*

Dosage and Administration

For primary hyperaldosteronism: *400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.*

For edema in adults: *Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.*

For edema in children: *Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.*

For essential hypertension: *Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.*

For hypokalemia: *25 to 100 mg. daily in divided doses.*

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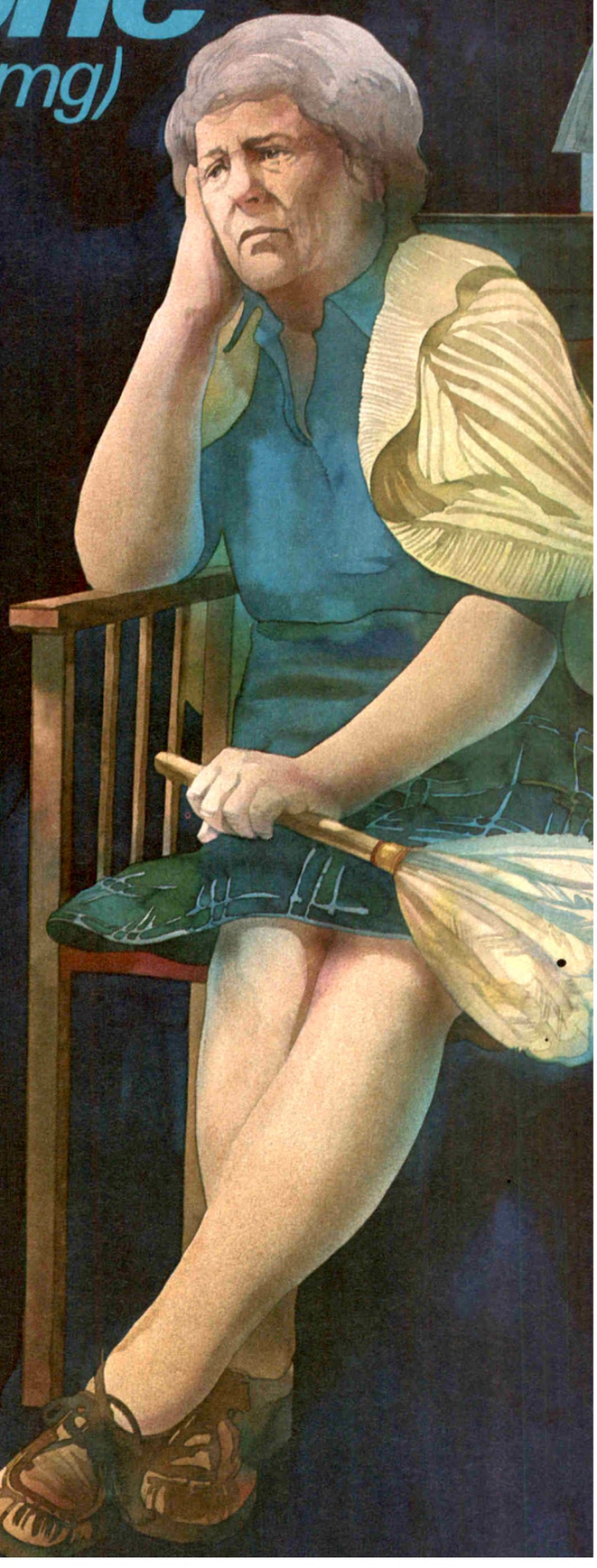

"Round-the-house" edema, electrolyte washout, subtle secondary volume buildup

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☑ *The unique potassium-regulating mechanism of Aldactone can prevent hypokalemia with limited risk of hyperkalemia. This helps protect your patient from digitalis-induced arrhythmias.*

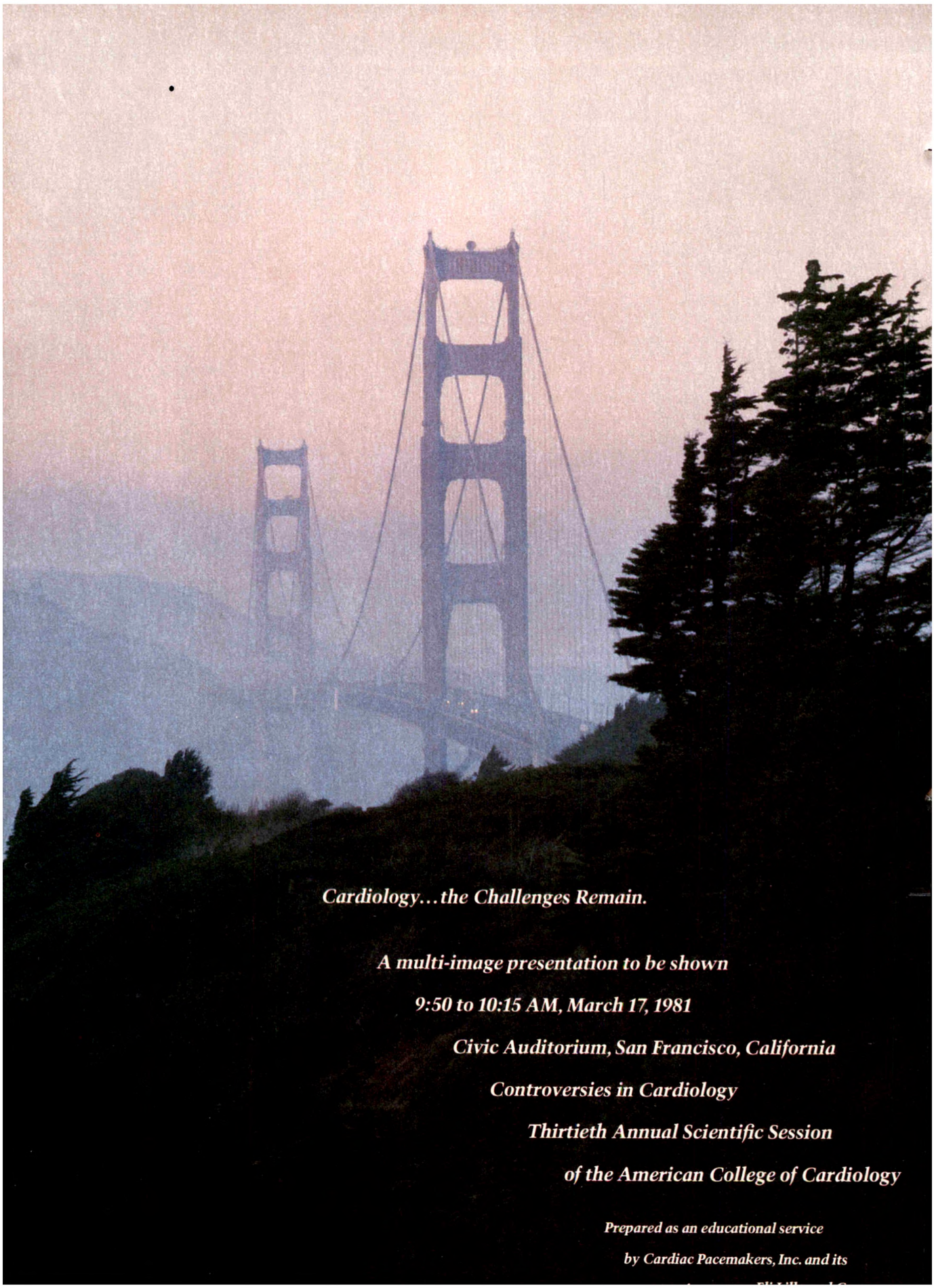
☑ *Unlike other potassium-sparers, Aldactone specifically antagonizes aldosterone, thereby mitigating secondary volume buildup.*

For these reasons, Aldactone is a valuable adjunct in the treatment of CHF.

Limitations to Consider: *Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus, Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and* Warnings *section of Aldactone prescribing information.)*

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the preceding page.

SEARLE *Searle & Co.*
San Juan, Puerto Rico 00936



Cardiology…the Challenges Remain.

A multi-image presentation to be shown

9:50 to 10:15 AM, March 17, 1981

Civic Auditorium, San Francisco, California

Controversies in Cardiology

Thirtieth Annual Scientific Session

of the American College of Cardiology

Prepared as an educational service

by Cardiac Pacemakers, Inc. and its

Continued Gains in Hypertension*

EDWARD D. FROHLICH, MD, FACC

New Orleans, Louisiana

During the decade of the 1970s dramatic achievements were realized in the field of hypertension. The prior decade witnessed the introduction of a remarkable array of antihypertensive therapeutic agents: diuretic drugs, beta adrenergic receptor blocking drugs, other sympathetic inhibitors and oral and parenteral vasodilators. The impact of these major achievements in therapy is still being appreciated in other areas of cardiovascular medicine (for example, vasodilating therapy for heart failure).

Treatment of Hypertension in the 1970s

The first fruits from these contributions were the data reported from the Veterans Administration Cooperative Studies on hypertension, ably led by Edward D. Freis.[1–3] These studies conclusively demonstrated the merits of systematic antihypertensive drug therapy in reducing morbidity and mortality from the complications of hypertensive cardiovascular disease in patients whose diastolic blood pressure exceeded 104 mm Hg. As a result of this landmark study, Elliot Richardson, the then Secretary of Health, Education, and Welfare, and Theodore Cooper established the High Blood Pressure Education Program and permitted the granting of funds for the Hypertension Detection and Follow-Up Program.

The initial reports from the 5 year prospective study involving 14 medical centers and almost 11,000 treated patients were published at the end of the decade.[4,5] These studies indicated that vigorous treatment of female as well as male patients of all ages with diastolic pressure in excess of 90 mm Hg was associated with significant reduction in both cardiovascular and noncardiovascular mortality. Thus, the merits of vigorous pharmacologic antihypertensive therapy were established in the 1970s. The interested reader is referred to these now-classic cardiovascular therapeutic documents[1–5] for details of these studies; this is not the purpose of the present editorial.

The reason for this communication is to draw attention to the most recent reports concerned with the ongoing saga of successes in hypertension. Total cardiovascular deaths have declined from 54 percent at the beginning of the 1970s to 50 percent at the end. This sharp break in the downslope of this mortality curve may be related temporally to the dissemination of a series of recommendations by a Joint National Committee of authorities concerned with the detection, evaluation and treatment of high blood pressure. To be sure, it is always unwise to attribute a cause of a multifactorial problem to one agent. The decade of the 1970s was associated not only with widespread implementation of the Joint National Committee's recommendations through the High Blood Pressure Education Program but also with a decline in cigarette smoking; greater public consciousness of dietary controls (caloric, animal fat and sodium intake, for example); widespread establishment of hospital coronary intensive care units; development of mobile ambulance services; and even the phenomenon of the 1970s—jogging. Nevertheless, when one closely scrutinizes the data, the reduction in death rate could be related importantly to the decline in mortality from strokes.[6] And if we know of one major risk factor related to this reduction, it surely would be control of the abnormally elevated arterial pressure.[7] Thus, we see the merits of a vigorous antihypertensive treatment program and the birth of a new era of cardiovascular medicine—preventive cardiology.[8]

Hypertension in the 1980s

And now we have entered into the 1980s. Already we have seen major contributions. First, we have learned

From the Alton Ochsner Medical Foundation and Ochsner Clinic, New Orleans, Louisiana. Dr. Frohlich is Representative of the American College of Cardiology to the High Blood Pressure Education Program Coordinating Committee. Manuscript received October 27, 1980, accepted November 19, 1980.

Address for reprints: Edward D. Frohlich, MD, Alton Ochsner Medical Foundation, 1516 Jefferson Highway, New Orleans, Louisiana 70121.

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

ıat pharmacologic control of arterial pressure is es-
ntial for patients with diastolic pressure in excess of
) mm Hg. This was shown by the compelling data of
ıe Hypertension Detection and Follow-up Program.
nd we now have further inklings from multinational
ıoperative studies indicating that antihypertensive
ıerapy may be expected to reduce morbidity and
ortality from events related to ischemic heart disease.
he first report from Australia has recently been pub-
ıhed,[9] and we can anticipate similar reports from Great
ritain, Scandinavia and the United States.

A revised report from the Joint National Committee
ıs just been published presenting in detail the current
inking of experts concerned with detection, evaluation
ıd management of patients with hypertension.[10] And
ıcause the lower limit of diastolic pressure elevation recommended for treatment has been reduced from 105 to 90 mm Hg, we now include among the potential beneficiaries of therapy upwards of 54—not 23—million Americans.

The American College of Cardiology is pleased with its role in this success story. The College is a charter member of the High Blood Pressure Education Program and has been ably served on the Joint National Committee by a practicing cardiologist member and Joint National Committee vice-chairman; this physician, Dr. Marvin Moser, has been part-time consultant to the High Blood Pressure Education Program. We can anticipate, with great confidence, that with continued contributions in "preventive cardiology" the mortality rates from cardiovascular diseases will be reduced even further in the 1980s.

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10. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure: The 1980 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1980;140:1280–5.

The Laennec Bicentennial*

PAUL D. KLIGFIELD, MD

New York, New York

Cardiologists in the United States join with physicians around the world this month in remembering René Théophile Hyacinthe Laennec on the occasion of the bicentennial of his birth. Quite naturally, the inventor of the stethoscope remains honored in his native France, where many of the historic locations associated with the frail but energetic Breton who founded bedside chest diagnosis may be visited.

Laennec was born in February 1781 in Quimper, a port city in western Brittany. His birthplace along the Rue de Quai adjacent to the river Odet no longer exists, but an imposing memorial statue has been erected that overlooks the Place St. Corentin next to the town's great gothic cathedral. In Nantes, Laennec's childhood home still stands in the Place Buffay, the site of one of the Terror's most active guillotines. Although the old Hôtel Dieu of Nantes has been thoroughly modernized, a small room in the nearby medical school library has been dedicated to the discoverer of mediate auscultation and contains a fascinating exhibit of texts, portraits, manuscript material and personal memorabilia relating to Laennec. One of his residences in Paris stands unmarked at 23, Rue du Cherche Midi, a brisk walk from the Hôpital Necker, where in 1816, a rolled quire of paper served as the first stethoscope and where today, Laennec's achievement is commemorated by a plaque at the hospital's outer gate.

A short drive from Quimper leads to the wooded manor of Kerlouarnec, the country home near Ploaré to which Laennec frequently retired in ill health after publication of *De l'Auscultation Médiate* in 1819. It is now a private estate. Here, surrounded by his beloved Breton fields, Laennec died in 1826 at the age of 45. His simple grave may be visited in the nearby hillside cemetery along the road leading to Douarnenez. But clearly, his true memorial exists every time we examine a patient.

Insight into the personality of Laennec is available in the English translation of Kervran's biography,[1] which supplements more traditional accounts of his life and times.[2,3] The splendid comprehensive biography by Rouxeau[4,5] has not been translated. A recent facsimile of the 1821 English edition of Laennec's masterpiece is available[6] for those who wish to review his classic observations.

FIGURE 1. Statue of Laennec in the Place St. Corentin, Quimper.

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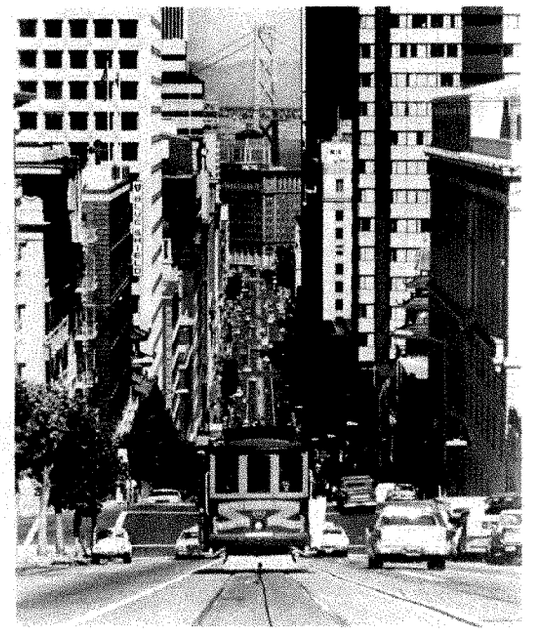
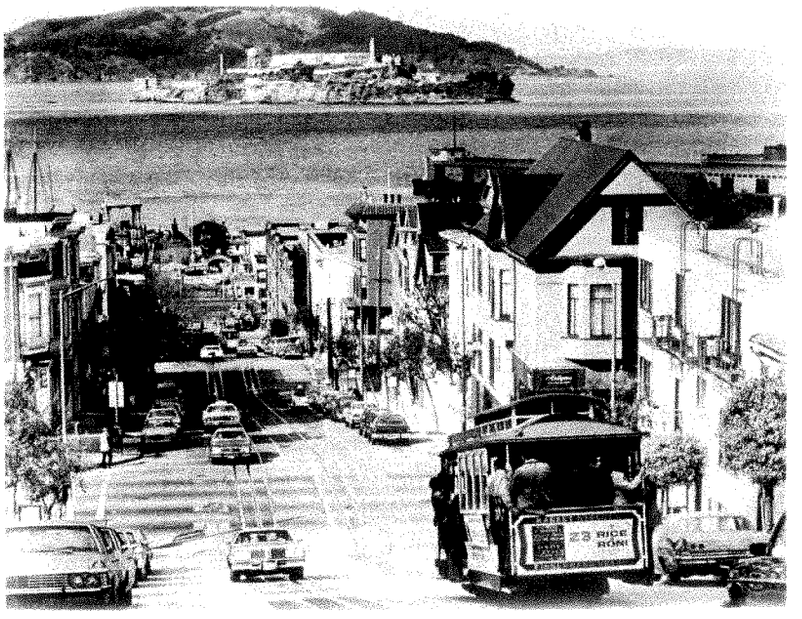
From the Department of Medicine, Division of Cardiology, New York Hospital Cornell Medical Center, New York, New York. Manuscript received November 20, 1980, accepted December 1, 1980.

Address for reprints: Paul D. Kligfield, MD, Department of Medicine, Division of Cardiology, The New York Hospital Cornell Medical Center, 525 East 68 Street, New York, New York 10021.

* Editorials published by the Journal reflect the views of the authors and do not necessarily represent the views of the Journal or of the American College of Cardiology.

American College of Cardiology 30th Annual Scientific Session
San Francisco, California March 15–19, 1981





Views from the host city. **Upper left,** California Street. **Upper right,** Japanese Tea Garden, Golden Gate Park. **Lower right,** looking down Russian Hill to the National Maritime Museum at Aquatic Park. Photographs courtesy of San Francisco Convention & Visitors Bureau.

INVITATION FROM THE PRESIDENT

It is a privilege for me to extend a personal invitation to you and your family to attend the 30th Annual Scientific Session of the College in San Francisco, March 15–19, 1981.

The Scientific Program Committee, Co-chaired by Drs. Emilio Giuliani and Dwight McGoon, have developed a broad comprehensive program that will have areas devoted to the entire spectrum of cardiovascular disease, from the basic sciences to diagnosis, management, and prevention. Mini-Courses, Core Curricula, Self-Assessment, Symposia, Luncheon and Fireside Panels, and Meet the Experts sessions will enable you to hear and have involvement with recognized experts. Progress and new knowledge will be reflected in the sessions of submitted papers on original investigation, the sessions on Controversies in Cardiology, and in the special lectures.

Doctor Hilliard J. Katz is in charge of local arrangements with the marvelous ambience of San Francisco as his backdrop. He and the members of his committee have proposed some interesting and unique programs that will reflect the cosmopolitan and cultural features of the great western city.

I look forward to seeing you and welcoming you to this 30th Annual Scientific Meeting of our College. I am certain you will find it stimulating and scientifically challenging. In addition, you will find the social and cultural aspects outstanding.

Robert O. Brandenburg, MD, FACC
President, 1980–81
American College of Cardiology

GREETINGS FROM SAN FRANCISCO

I am pleased to report that plans for the 30th Annual Scientific Session of the American College of Cardiology in San Francisco are rapidly developing in an effort to surpass the success of the 1973—22nd Annual Scientific Session held in our favorite city by the Golden Gate. San Francisco needs no introduction as one of the world's most attractive cities with unmatched cultural, culinary and geographic opportunities for delightful visiting and enjoyment. The Golden Gate Bridge, Chinatown, Japanese Tea Gardens, Fisherman's Wharf, Nob Hill Fine Arts Museums and Performing Arts Center all are part of our fascinating city.

A stimulating Hospitality Program provides varied opportunities to visit many of the outstanding local attractions such as half or full day tours to the famous Flower Mart and Orchid Farms, and to Victorian, traditional and modern homes, as well as ferry boat trips and architectural walks. Additional offerings of visits to the various ethnic areas of the city will be available. The program will also provide in-house lectures with wide appeal.

I look forward to seeing you in San Francisco.

Hilliard J. Katz, MD, FACC
Chairman, Local Arrangements Committee
30th Annual Scientific Session

REMARKS FROM THE SCIENTIFIC PROGRAM COMMITTEE

The Scientific Program Committee cordially welcomes you to the 30th Annual Scientific Session of the American College of Cardiology. In this age of rapidly expanding knowledge of the heart and improving management of its diseases, the Annual Program of the College should overview the entire broadly advancing field, look more deeply into specific areas of interest, and provide the means for dialogue at all levels. To this end, a wide variety of educational sessions has been arranged.

The *Core Curricula* run throughout the program, bringing to the practitioner comprehensive current knowledge relevant to modern approaches to specific clinical problems. The *Symposia,* also scheduled for each day of the program, provide in-depth analyses of a wide variety of specifically focused topics. The greater informality and variety of *Luncheon* and *Fireside Panels* are designed to facilitate interchange between the panel of experts and their audiences concerning a broad range of practical problems. The ultimate opportunity for dialogue is provided by the *Meet the Experts* sessions, wherein a pair of authorities visit openly with a small group of attendees. Considerable excitement surrounds the *Controversies in Cardiology*—debates about timely but unsettled issues. Because of its popularity, this year two sessions of *Controversies* are planned, rather than one as in years past. The program this year has been expanded to allow presentation of even more *Original Contributions* by leading workers from around the world. These sessions are grouped into broad categories of interest. Additional high points of the program are the *Young Investigators Awards Competition,* the *Self-Assessment* program, the *Opening Plenary Address* (*Franz Groedel Lecture*), and the *Louis F. Bishop Lecture.*

Still another excellent opportunity to expand the educational experience of the Annual Meeting is provided on the Sunday prior to the formal Scientific Sessions, in the form of *Mini-Courses.* These are in-depth workshops on a variety of timely areas of interest.

The Scientific Program Committee earnestly hopes that its efforts to organize this ambitious program will prove to be rewarding to each participant and each person in attendance. If so, the credit will belong to the expertise, cooperation, and selfless dedication of the members of the Committee, the many session Chairmen and others who have given invaluable advice, President Brandenburg who worked closely with the Committee, the staff of the College, and Julianne E. Osborn, Program Coordinator.

The 1981 Scientific Program Committee: Robert O. Brandenburg, MD; C. Richard Conti, MD, Coordinator of Luncheon and Fireside Panels: Jesse E. Edwards, MD; Richard E. Kerber, MD, Coordinator of Core Curricula sessions; Richard P. Lewis, MD; Dan G. McNamara, MD; Eldred D. Mundth, MD, Coordinator of Controversies in Cardiology sessions; Jacqueline A. Noonan, MD, Coordinator of Mini-Courses; Bertram Pitt, MD; Charles E. Rackley, MD; Richard O. Russell, Jr., MD; James Scheuer, MD, Coordinator of Meet the Experts sessions; James A. Shaver, MD, Coordinator of Symposia sessions; Arnold M. Weissler, MD.

Emilio R. Giuliani, MD, FACC
Co-Chairman, 1981 Scientific Program Committee

Dwight C. McGoon, MD, FACC
Co-Chairman, 1981 Scientific Program Committee

THIRTIETH ANNUAL SCIENTIFIC SESSION
GENERAL INFORMATION

Every effort has been made to organize the 1981 Annual Meeting in such a way that it provides a productive and worthwhile experience for all in attendance.

San Francisco Registration Schedule

General Registration:

San Francisco Hilton Hotel

Date	Hours
Saturday, March 14	1:00 p.m.–6:00 p.m.
Sunday, March 15	7:00 a.m.–6:00 p.m.

Main Lobby, Civic Auditorium

Date	Hours
Monday, March 16	7:00 a.m.–5:00 p.m.
Tuesday, March 17	8:00 a.m.–5:00 p.m.
Wednesday, March 18	8:00 a.m.–5:00 p.m.
Thursday, March 19	8:00 a.m.–12:00 Noon

Hospitality Registration:

Beginning at 8:00 a.m., Sunday, March 15 in the Georgian Room Foyer of the Hotel St. Francis.

Registration Fee

There is no registration fee for the members of the American College of Cardiology, program participants and scientific exhibitors. Non-member fee is one hundred and fifty dollars. Medical students, interns, residents, fellows, nurses, and technicians may attend without fee as guests of the American College of Cardiology **upon presentation of a letter of certification.** (Letter of certification **must** accompany advance registration card. If registering at the meeting, letter of certification **must be shown** to personnel at registration counter in San Francisco.)

Requests for refund of registration fee, Mini-Courses, Meet the Experts, Luncheon or Dinner-Dance will be honored if received in the College office in writing by Friday, February 27, 1981.

Presentation of Submitted Papers

Ten minutes for presentation and three minutes for discussion is the time limit for each paper.

Continuing Medical Education Credit

As an organization accredited for continuing medical education, the American College of Cardiology certifies that this continuing education offering meets the criteria for 20 1/2 credit hours in Category 1, provided it is used and completed as designed. For credit which may be acceptable to state medical associations, specialty societies, or state boards of medical licensure, please contact those organizations.

Each Luncheon Panel attended meets the criteria for 1 credit hour in Category 1.
Each Mini-Course attended meets the criteria for 3 credit hours in Category 1.
Each Fireside Panel attended meets the criteria for 1 1/2 credit hours in Category 1.

Luncheon Panels

Seating is limited at these sessions; therefore, early reservation of luncheon tickets is advisable. **Admission to the luncheon panel discussion is by ticket only.** The Advance Registration Form provides for the reservation of your choice.

Mini-Courses

Registration is limited for each course; therefore, early reservation of Mini-Course tickets is essential to assure a place in the subject of your choice. **Admission to the Mini-Courses is by ticket only.** The Advance Registration Form provides for the reservation of your choice.

Fireside Panels

The Fireside Panels will be held in the Hotel St. Francis and the San Francisco Hilton Hotel. Tickets are not required for Firesides. Attendance is, however, limited to the seating capacity of the room.

Self-Assessment Program

The 1981 Self-Assessment Program will be offered Monday, Tuesday, and Wednesday from 8:00 a.m. to 5:00 p.m., and Thursday from 8:00 a.m. to 12:00 Noon. The program will require 50 minutes.

"MEET THE EXPERTS"

These workshops provide a forum for person-to-person discussion of a variety of cardiovascular problems. Registration is limited for each Meet the Experts group. **Admission is by ticket only,** therefore, early reservation of the Meet the Experts tickets is advisable. The Advance Registration Form provides for the reservation of choice. Participants are assumed to have a basic understanding of the topics discussed at the workshops and are encouraged to bring applicable tracings or problems for group discussion.

Monday, March 16

Group I	10:30 a.m.–11:30 a.m.
Group I	2:30 p.m.–3:30 p.m.
Group II	4:00 p.m.–5:00 p.m.

Tuesday, March 17

Group I	9:00 a.m.–10:00 a.m.
Group II	10:30 a.m.–11:30 a.m.
Group I	2:30 p.m.–3:30 p.m.
Group II	4:00 p.m.–5:00 p.m.

Wednesday, March 18

Group I	9:00 a.m.–10:00 a.m.
Group II	10:30 a.m.–11:30 a.m.
Group I	2:00 p.m.–3:00 p.m.

Thursday, March 19

Group I	9:00 a.m.–10:00 a.m.
Group II	10:30 a.m.–11:30 a.m.

Technical and Scientific Exhibits

More than 500 exhibits will be featured at the 30th Annual Scientific Session. The 1981 exhibits are designed to update the physician's knowledge of products and research and they deserve the attention of all physicians and scientists in attendance. Exhibit hours are:

Date	Hours
Monday, March 16	9:00 a.m.–5:00 p.m.
Tuesday, March 17	9:00 a.m.–5:00 p.m.
Wednesday, March 18	9:00 a.m.–5:00 p.m.
Thursday, March 19	9:00 a.m.–12:00 Noon

Transportation

Shuttle bus service will be provided at regular intervals for all registrants to and from the San Francisco Civic Auditorium and all hotels in the official College commitment. Schedules and routes will be posted in the main lobbies of all hotels within the College commitment and will also be listed in the final program.

Joggers

There will be a jogging tour led by Past President Henry D. McIntosh, MD, FACC, come rain or shine on Monday, Tuesday, and Wednesday mornings. Departure will be at 6:30 a.m. from the Union Square entrance to the St. Francis Hotel.

At 7:00 a.m., there will be a cool-down continental breakfast served in the California East Room of the St. Francis. We look forward to seeing you each of the three days.

Fellowship Candidates

Fellows who are to be inducted at the 1981 Convocation will receive separate instructions. Please remember that you must sign the Convocation Register prior to 10:00 a.m. on Wednesday, March 18, 1981. The Register will be located on the second floor of Civic Auditorium.

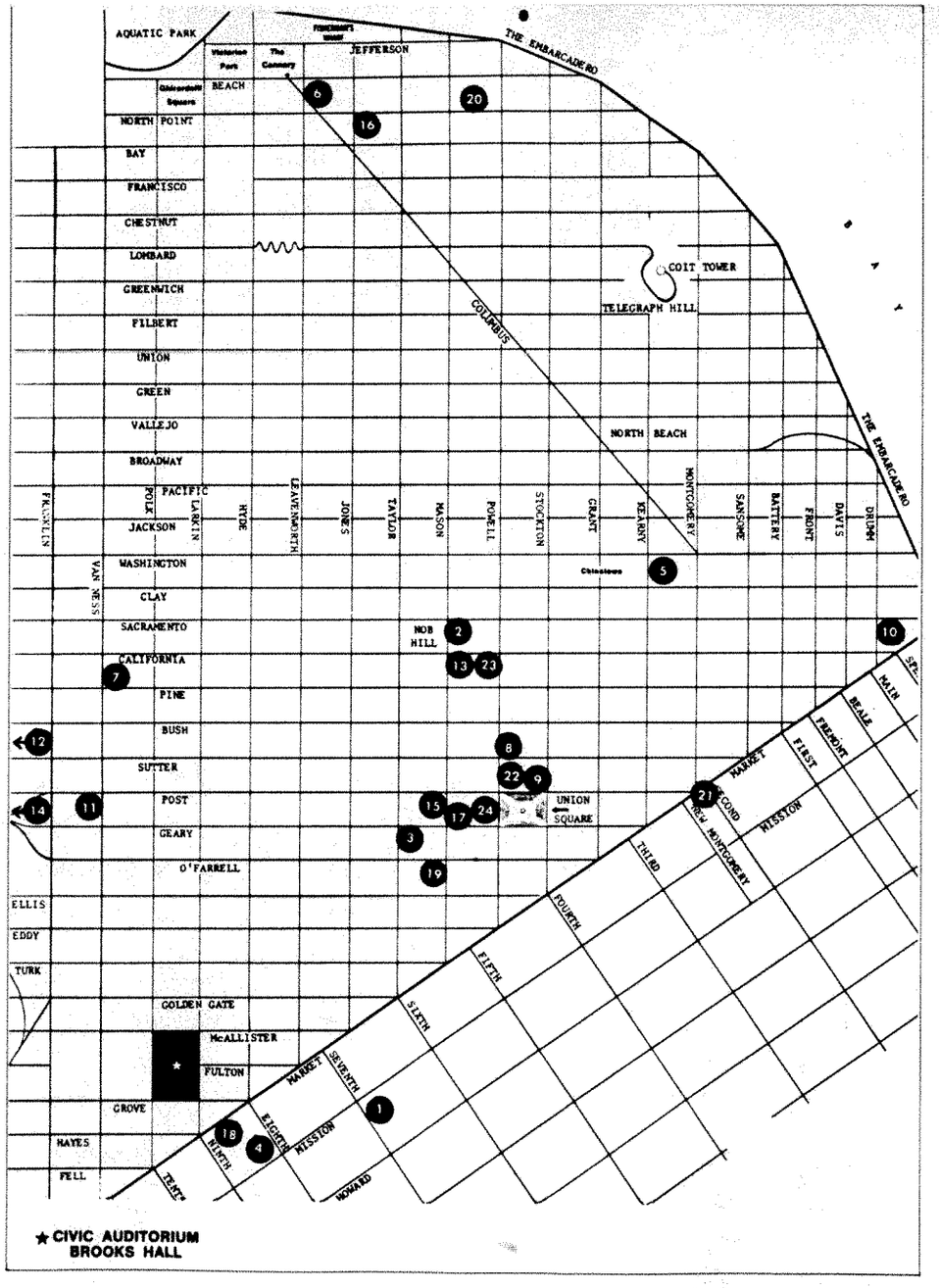
Application for Hotel Accommodations

A map and application form for hotel accommodations are shown on pages 384 and 385. Please note:

1. The form must be received by the Housing Bureau **no later than February 12** to ensure receipt of a written confirmation.
2. **After February 12,** the Housing Bureau may be contacted directly to determine availability of rooms. After contacting the Bureau at 415 626-5500, you must then contact the hotel directly to make your reservation.

For more information contact:

Ellen Nitzberg, Assistant Director
Annual Scientific Session Department
American College of Cardiology
9111 Old Georgetown Road
Bethesda, Maryland 20014
(301 897-5400).



The following are hotels in San Francisco, where reservations are available. Please refer to number and map for location.

MAP LOC	HOTEL	SINGLES	DOUBLES/ TWINS	SUITES
1	Americania Motor Lodge	$47/$57	$49/$66	$62/$80
2	Fairmont Hotel	$78/$125	$98/$145	$225/$495
3	Four Seasons Clift Hotel	$84/$132	$104/$152	$170/$400
4	Holiday Inn/Civic Center	$48	$58	
5	Holiday Inn/Financial District	$65/$75	$77/$87	
6	Holiday Inn/Fisherman's Wharf	$70/$82	$82/$94	$150/$260
7	Holiday Inn/Golden Gateway	$56/$68	$68/$80	$144/$209
8	Holiday Inn/Union Square	$70/$98	$82/$112	$175/$450
9	Hyatt on Union Square	$85/$105	$95/$115	$250/$600
10	Hyatt Regency	$75/$95	$95/$115	$275/$640
11	Jack Tar Hotel	$65	$75	$175/$250
12	Kyoto Inn	$42/$45	$49/$52	$89/$130
13	Mark Hopkins Hotel	$75	$95	$210/$330
14	Miyako Hotel	$62/$80	$80/$98	$200/$225
15	Pacific Plaza Hotel	$70/$80	$85/$95	$150/$250
16	Ramada Inn/Fisherman's Wharf	$66	$86	$125/$200
17	Raphael Hotel	$50/$64	$62/$76	
18	San Franciscan Hotel	$50/$65	$58/$67	$95/$260
19	San Francisco Hilton—Main Bldg (Co-headquarters)	$53/68/78 $88/$98	$71/86/96 $106/116/126	$194/$369
	Tower	$78/88/98 $108	$96/106/116 $126	
20	Sheraton/Fisherman's Wharf	$73	$83	
21	Sheraton Palace Hotel	$58/$86	$69/$98	$145/$203
22	Sir Francis Drake Hotel	$55/$85	$65/$95	$185/$225
23	Stanford Court	$98/$130	$118/$150	$200/$375
24	St. Francis Hotel—Main Bldg. (Co-headquarters)	$50/55/60 $73/$95	$65/70/80 $93/$120	$180/$1,100
	Tower	$90/105/120	$115/130/145	

APPLICATION FOR HOTEL ACCOMMODATIONS

Please type or PRINT in black ink.

Send Confirmation to:

NAME

ADDRESS

CITY & STATE

ZIP CODE TELEPHONE

Please make reservations at:

1st Choice

2nd Choice

3rd Choice

4th Choice

MAIL APPLICATION TO:

ACC Housing Bureau
c/o San Francisco Convention and Visitors Bureau
1390 Market Street
San Francisco, California 94102

Please reserve the following accommodations: (Please type or print plainly, in black ink.)

Rooms		Names of Occupants	Arrival Date and Time	Departure Date	*Guarantee (Please Check)
Type	Rate				
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(Please make copies of this form if more than 10 rooms are required.)

ROOM TYPE: S —Single—Occupancy by one person
T —Twin—Two persons/two beds
D —Double—Two persons/one bed
P+1—Parlor + one bedroom
P+2—Parlor + two bedrooms

*A guaranteed reservation will be held for late arrival. However, you will pay for the first night's lodging even if you do not occupy the room — UNLESS you cancel your reservation 24 hours in advance.

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the Continuing Education Committee for Extramural Programs assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The Continuing Education Committee for Extramural Programs of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

FEBRUARY THROUGH AUGUST 1981

1981

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

FEB. 2–4 — **Clinical Echocardiography 1981—M-Mode, 2-Dimensional and Pulsed Doppler Techniques,** Pravin M. Shah, FACC, director and John S. Child, FACC, Joseph K. Perloff, FACC, and Maylene Wong, co-directors. Sheraton Harbor Island Hotel, San Diego, CA

FEB. 9–11 — **Calcium (Slow Channel)-Inhibiting Drugs in Cardiovascular Therapy: Mechanism of Action and Application.** Borys Surawicz, FACC and Attilio Maseri, FACC, directors. New Orleans Marriott, New Orleans, LA

FEB. 19–20 — **Ventricular Arrhythmias and Sudden Cardiac Death.** Thomas B. Graboys, FACC and Bernard Lown, FACC, directors. Sheraton Boston Hotel, Boston, MA

MAR. 30–APR. 3 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Krannert Institute of Cardiology, Indiana University Medical Center, Indianapolis, IN

APR. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 16–18 — **New Diagnostic and Therapeutic Modalities in Cardiology.** Edmund H. Sonnenblick, FACC and James Scheuer, FACC, directors. Grand Hyatt New York, New York, NY

APR. 23–24 — **Contemporary Phonocardiography (With Echocardiographic Correlation).** Morton E. Tavel, FACC, director. Methodist Hospital, Indianapolis, IN

APR. 27–MAY 1 — **Consultant's Course in Cardiology.** Richard Gorlin, FACC, Louis E. Teichholz, FACC, Simon Dack, FACC and Ephraim Donoso, FACC, directors. Mount Sinai Medical Center, New York, NY

APR. 29–MAY 1 — **Vectorcardiography—An Advanced Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

MAY 7–9 — **The Pathology of Acquired Diseases of the Heart and Conduction System.** Jesse E. Edwards, FACC, Maurice Lev, FACC and Saroja Bharati, FACC, directors. Radisson Hotel, St. Paul, MN

MAY 7–9 — **Cardiac Emergencies.** Arthur Selzer, FACC and Richard Pasternak, co-directors. The Mark Hopkins, San Francisco, CA

MAY 7–9 — **Practical Cardiology for the Primary Care Physician,** Leonard S. Dreifus, FACC and Joel Morganroth, FACC, directors. Sarasota Hyatt Hotel, Sarasota, FL

MAY 13–15 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director and Antonio C. de Leon, Jr., FACC and John F. Stapleton, co-directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington DC

MAY 14–16 — **Cardiac Diagnostic Techniques—A Clinical Perspective.** Arnold M. Weissler, FACC and Nicholas Z. Kerin, FACC, directors and Franklin E. Hull, FACC, S. C. Khullar, FACC and Melvin Rubenfire, FACC, co-directors. Detroit Plaza Hotel, Renaissance Center, Detroit, MI

MAY 18–22 — **Modern Cardiology.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Sheraton Atlanta Hotel, Atlanta, GA

MAY 28–31 — **Sixth Annual Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

JUNE 17–19 — **The Patient with Arrhythmia—A Clinical Approach.** Ross D. Fletcher, FACC and W. Proctor Harvey, FACC, directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington, DC

JUNE 30–JULY 3 — **Eighth Annual Symposium on Clinical Echocardiography: Current Applications and New Developments.** Arthur D. Hagan, FACC, director and Anthony N. DeMaria, FACC and William F. Friedman, FACC, co-directors. Snowbird Conference Center, Snowbird Ski and Summer Resort, Snowbird, UT

AUG. 29–31 — **Tutorials in the Tetons: Clinical Cardiology: Diagnostic and Therapeutic Advances (Seventh Annual).** Robert S. Eliot, FACC, director and James C. Buell, Timothy Fleming, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

EARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's Learning Center is located at the College's headquarters in Bethesda, Maryland. The purpose of the Learning Center is to support professional commitment to quality patient care by providing a standard of excellence in continuing medical education.

For additional information or a complete program calendar, contact the Program Registrar, Heart House Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

LEARNING CENTER PROGRAMS: FEBRUARY to JULY 1981

Program Number	Date	Program Director	Title of Program
334	February 5–6	August M. Watanabe, MD	Fundamental Cardiac Biochemistry for the Cardiologist
333	February 12–14	H. J. C. Swan, MD	Newer Concepts and Directions in the Treatment of Heart Failure Associated with Coronary Heart Disease
310	February 16–18	Sylvan Lee Weinberg, MD	Clinical Update for Nurses: The Coronary Care Unit and Acute Myocardial Infarction
311	February 23–25	William C. Roberts, MD	Congenital Heart Disease: The Multidisciplinary Approach
312	March 2–4	Nanette K. Wenger, MD	Rehabilitation of the Cardiac Patient
313	March 30–31	Jere H. Mitchell, MD	Cardiovascular Benefits and Risks of Exercise
314	April 1–3	J. O'Neal Humphries, MD	Coronary Heart Disease: New Management Methods
315	April 8–10	Victor Parsonnet, MD	Current Concepts in Pacing
316	April 13–15	Keith Cohn, MD	Exercise Testing: Diagnostic and Physiological Considerations
317	April 20–22	Pravin M. Shah, MD	Current Applications of Echocardiography: M-Mode, Two-Dimensional and Pulse Doppler Techniques
318	April 23–25	Daniel S. Berman, MD	Nuclear Cardiology
319	April 27–28	Leonard S. Dreifus, MD and Frits L. Meijler, MD	Computer Electrocardiology: Present Status and Hope for the Future
320	April 30, May 1–2	John A. Spittell, MD	Peripheral Vascular Disease
321	May 6–8	Marvin I. Dunn, MD	Electrocardiography for Critical Care Nurses
322	May 11–13	Abdul J. Tajik, MD and James B. Seward, MD	The Role of Two-Dimensional Echocardiography in the Clinical Practice of Cardiology
323	May 14–16	G. Charles Oliver, MD	Ubiquitous PVC
324	May 18–20	William J. Mandel, MD	His Bundle Electrocardiography: Contributions to the Clinical Understanding of the Electrocardiogram
325	May 28–29	Robert O. Brandenburg, MD	Cardiology for the Consultant
326	June 1–3	Shahbudin H. Rahimtoola, MD	Valvular Heart Disease
328	June 8–10 (tentative)	Borys Surawicz, MD	Changing Role of Electrocardiography in the Clinical Practices
327	June 11–13	Robert G. Tancredi, MD	Management of Pulmonary, Renal and Electrolyte Disorders in Cardiac Patients
329	June 15–17	Robert A. O'Rourke, MD	Detection of Cardiac Disease by Physical Examination
302	June 22–24	Paul C. Gillette, MD	Decisions in Clinical Pediatric Cardiac Surgery
331	June 29–30, July 1	B. Leonard Holman, MD	Nuclear Cardiology
330	July 8–10	Michael R. Rosen, MD	Clinical Pharmacology and Electrophysiology of Antiarrhythmic Drugs

IN MEMORIAM: MARIANO ALIMURUNG, MD, FACC

On Sunday night, November 16 or Monday morning, November 17, a man was murdered in his hotel room by strangulation by a thief. That story and similar madness can be found in each day's news. This man was a special friend, not only of myself but of the United States, of international medicine and cardiology, of the American College of Cardiology, and all who knew him. He was Dr. Mariano Alimurung from The Philippines, in the United States as he has been so many times for heart meetings, this time the annual meeting of the American Heart Association in Miami, Florida. On the last evening of his life, he had dinner with old friends, Dr. and Mrs. Louis Lemberg, returned to his hotel and, it is assumed, surprised someone ransacking his room and was killed, defending himself.

Dr. Alimurung was trained by Paul White and was first here in the United States in 1947. He was the first governor for the College in The Philippines and the host of the College's first circuit course. In 1973 Dr. Alimurung was made a Distinguished Fellow of the College. His affection for this country and its people brought him here yearly, and hundreds of us have been under his vigorous guidance in Manila. Vigorous is the only way to describe the happy, wholehearted, gracious enthusiasm with which he took over the management of one's visit.

The utter meanness that ended the life of this friend of Americans is awful. No logic, no imagination, no justification can make clear why this special man had to lose his life while carrying on one more act of the medical ambassadorship which he made his life's work. Mariano Alimurung was equally a citizen of both countries and few physicians were such complete internationalists. The sorrow in his passing is a sorrow felt by men and women of cardiology in every nation. A fitting farewell to him does not need to list degrees, honors, awards, officerships, academic posts, editorships and papers, for all who read these notes have their special memory of the very human qualities that made Mariano the unusual man he was.

Dr. Alimurung **(left)** *with Past College Presidents Eliot Corday* **(center)** *and E. Grey Dimond* **(right).**

To his wife Natividad and to their children and to his colleagues in The Philippines, we Americans send a message of profound grief, sympathy and, above all, an apology for his unjust end on American soil.

E. Grey Dimond, MD, FACC

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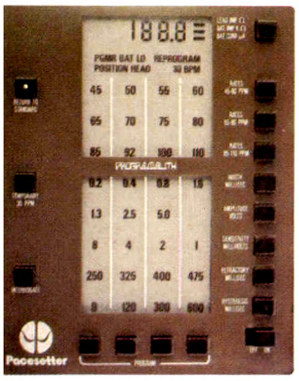
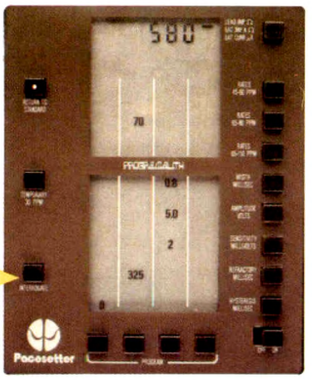
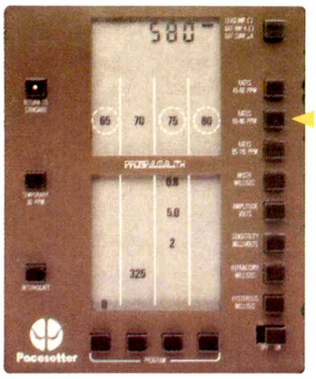


urn on the programmer. The display creen flashes and then fully illumi- ates as the programmer performs a ystem self-check.



Press "Interrogate" button. Telemetry confirmation of programmed settings and measured data will appear on the display screen.



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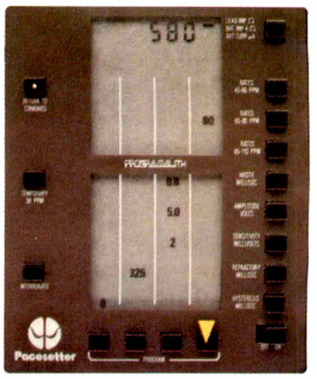

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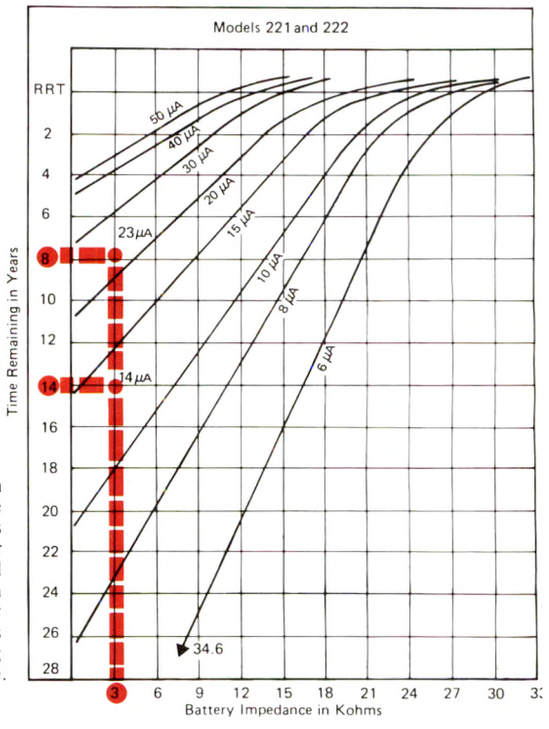

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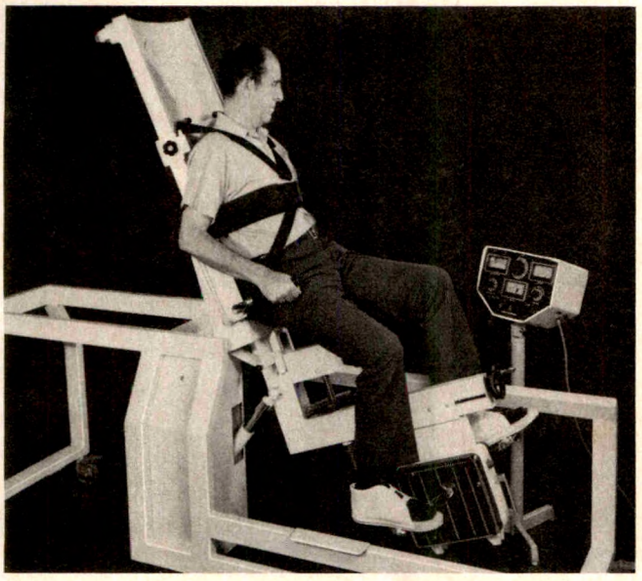
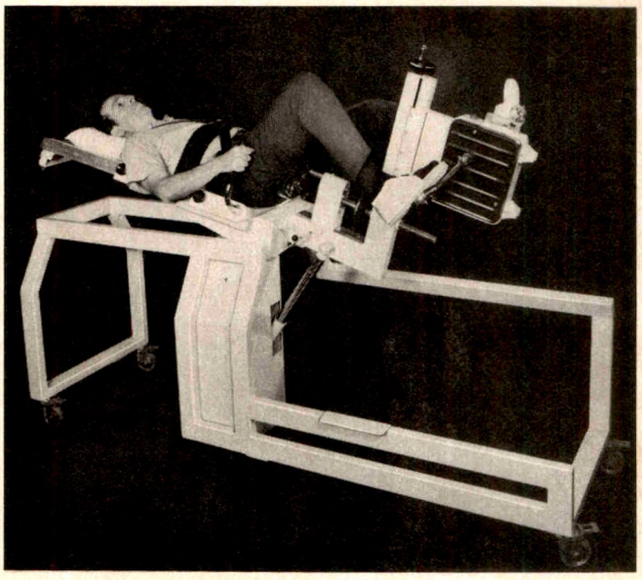


Erect stress test position.



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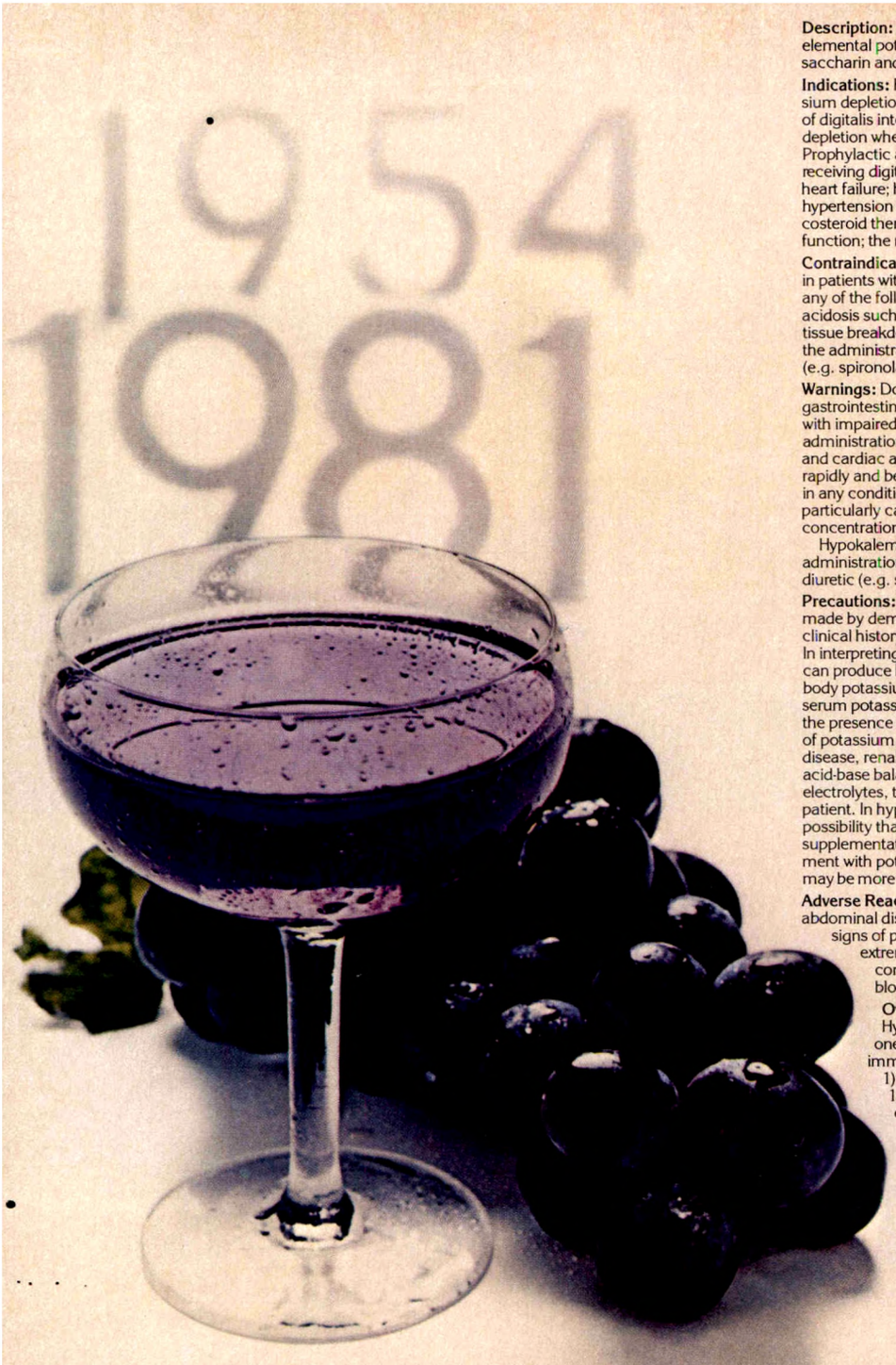

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Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g. spironolactone, triamterene).

Warnings: Do not administer full strength. Kaon Elixir may cause gastrointestinal irritation if administered undiluted. In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in any condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

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Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient. In hypokalemic states, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In these circumstances, potassium replacement with potassium chloride (e.g. Kaochlor 10% Liquid, W-T) may be more advantageous than with other potassium salts.

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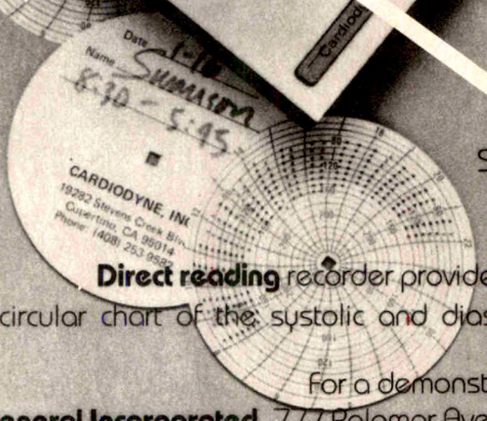

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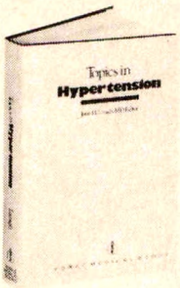

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CONTRAINDICATIONS:
Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine.

Partial A-V or complete heart block, or intraventricular conduction defects, especially those exhibiting a marked grade of QRS widening.

Renal disease resulting in significant azotemia, or those developing cardiotoxic effects such as conduction defects, ventricular premature beats, ventricular tachycardia or flutter while on the drug.

Marked cardiac enlargement, particularly with congestive failure, poor renal function, and especially renal tubular acidosis.

Idiosyncrasy or hypersensitivity to quinidine.

WARNINGS:
In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio resulting in an extremely rapid ventricular rate.

PRECAUTIONS:
The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication. The potential disadvantages and benefits must be weighed.

It should be administered cautiously, if at all, to senile patients.

Hospitalization for close clinical observation, electrocardiographic monitoring, and possibly plasma quinidine levels is indicated when large doses are used or with patients who present an increased risk.

ADVERSE REACTIONS:
Symptoms of cinchonism, ringing in ears, headache, nausea, disturbed vision may appear in sensitive patients after a single dose of the drug.

Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism, hypotension.

Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea.

Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision fields, photophobia, diplopia, night blindness, scotomata), optic neuritis.

Dermatologic: Cutaneous flushing with intense pruritus.

Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

See package insert for full information.

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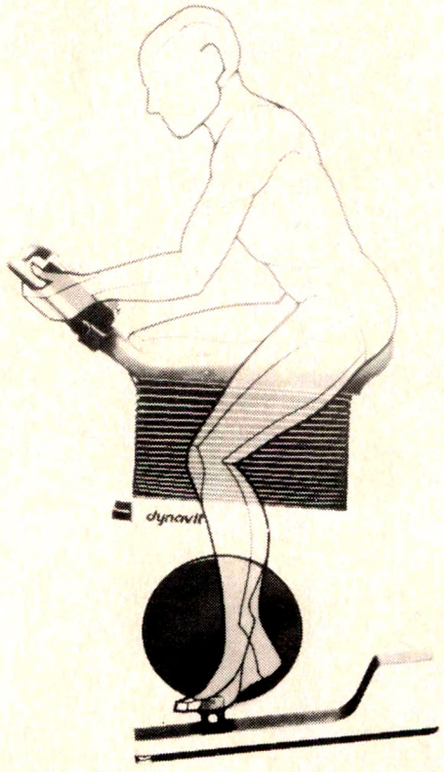
A dynamometer which measures physical work rates



Now with the new series of Dynavit equipment, graded exercise is possible on an ergometer with its own built-in calibrating dynamometer. Controlled pulses of current are fed through electrical windings of the braking system and a magnetic field is induced which becomes the braking torque to oppose the flywheel's rotation. The braking system is float mounted such that it responds in a counter torsion movement, and this is mechanically transmitted into a precision strain gauge.

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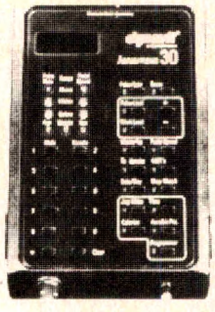
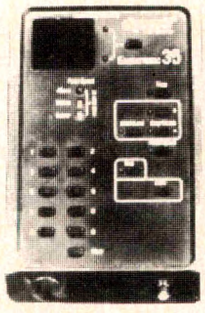


Aerobitronic 30



Ergometronic 35

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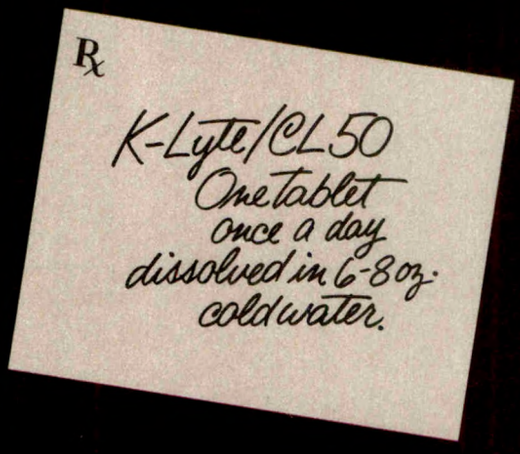

VESCENT TABLETS
E/CL® 50 mEq—Fruit Punch and Citrus Flavors
(effervescent tablet in solution supplies 50 mEq potassium chloride)

CRIBING CONSIDERATIONS

ATIONS: K-LYTE/CL 50 mEq is an oral potassium supplement for therapy or prophylaxis of potassium deficiency. It is particularly useful when e diuretics, corticosteroids, or severe vomiting and diarrhea cause excessive excretory potassium losses, and when dietary potassium is low. lly monitored, K-LYTE/CL 50 mEq may also be useful for potassium administration where digitalis intoxication results in cardiac arrhythmias.

RAINDICATIONS: Impaired renal function with oliguria or azotemia, Addison's disease, hyperkalemia from any cause.

INGS AND PRECAUTIONS: Since the amount of potassium deficiency may be difficult to determine accurately, supplements should be admin- with caution, and dosage adjusted to the requirements of the individual patient. Potassium intoxication rarely occurs in patients with normal function. Symptoms of potassium intoxication are variable. They include listlessness, mental confusion, and tingling of the extremities. Fre- checks of the clinical status of the patient, ECG, and serum potassium level are desirable. In established hypokalemia, attention should also ected toward other potential electrolyte disturbances. Potassium supplements should be given cautiously to digitalized patients and such ts should be monitored by ECG for cardiac irregularities. To minimize the possibility of gastrointestinal irritation associated with the oral inges- concentrated potassium salt preparations, **patients should be carefully directed to dissolve each dose completely in the stated nt of water.**

RSE REACTIONS: Nausea, vomiting, diarrhea, and abdominal discomfort may occur with the use of potassium salts.

GE AND ADMINISTRATION: Adults: 1 tablet completely dissolved 1 to 2 times daily, depending upon the requirements of the patient; 1 tablet q potassium chloride) in 6 to 8 ounces of cold or ice water. The normal adult daily requirement is approximately 50 mEq of elemental potassium. **It is suggested that K-LYTE/CL 50 mEq be taken with meals and sipped slowly over a 5-10 minute period.**

SUPPLIED: K-LYTE/CL 50 mEq effervescent tablets (fruit punch and citrus flavors) cartons of 30 and 100. Also available, K-LYTE/CL effer- nt tablets (25 mEq fruit punch and citrus flavors) cartons of 30 and 250. Each tablet is individually foil wrapped.

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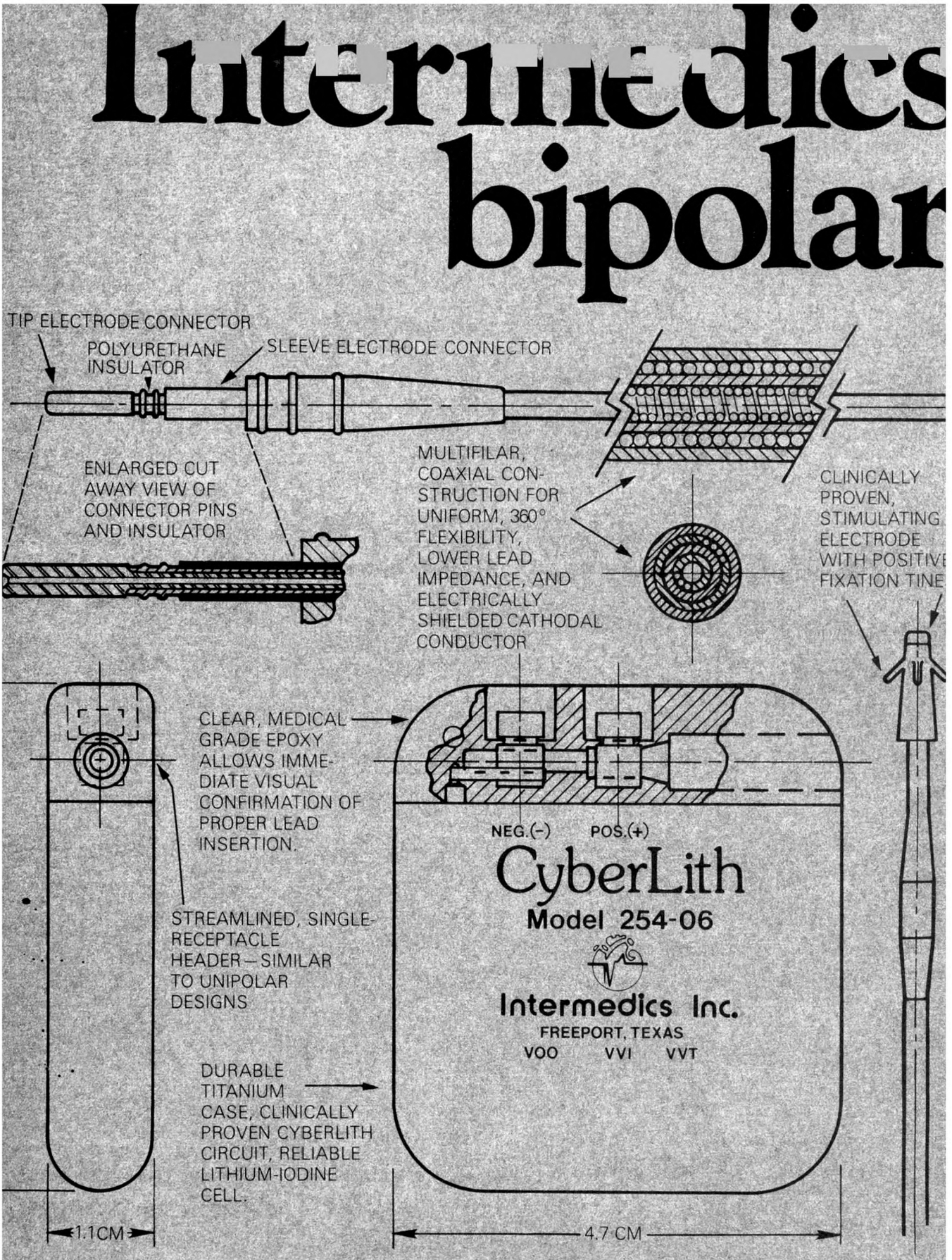
Intermedics bipolar



Intermedics Pulse Generators

INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to:

(1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet

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Intermedics in-line technology is an entirely new concept in bipolar pacing. It permits a bipolar pacing system to be as thin, small, and lightweight as most unipolar systems; it offers remarkable convenience and simplicity of use; and it provides unparalleled immunity to non-cardiac signals.

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Intermedics in-line bipolar concept has added an important dimension to the ability to reject undesired signals. The lead conductors are coaxial providing shielding all the way from the pulse generator to the ring electrode. The result is a clean, crisp intracardiac signal to the sensing circuitry of the pacemaker, free from unwanted noise or other artifacts. No other bipolar pacemaker available offers this advantage.

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The CyberLith I model 254-06, the newest member of the CyberLith family of pacemakers, is the first multiprogrammable pacemaker to use the new in-line technology. A simple, in-line connector eliminates the bulky, bifurcated connectors in the pacemaker and the lead. The smaller, physiologically compatible pacemaker fits easily in the pocket.

Intermedics—On The Leading Edge Of Pacemaker Technology.

Innovation is not the only reason for selecting an Intermedics product. The CyberLith family of pacemakers is unsurpassed in clinical experience, proven performance and reliability.

To find out more about the new convenience of bipolar pacing, contact your Intermedics representative or call us toll-free at 800/231-2330.

been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symotomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this de-

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The Pacekeeper™

For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.

CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm —whether with CARDIOQUIN Tablets or electroconversion — only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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ABSTRACTS

30th Annual Scientific Session

American College of Cardiology

March 15–19, 1981, San Francisco, California

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ANSWERS ABOUT ALDOMET® (METHYLDOPA|MSD)

Will an antihypertensive generally allow a normal cardiovascular response to exercise?

Cardiac output and blood pressure normally increase with increasing physical activity. ALDOMET does not significantly impair normal fluctuations of blood pressure during exercise.[1,2]

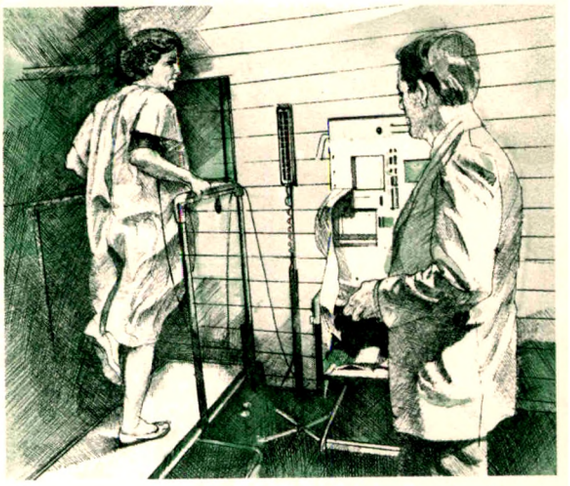
In a recent study of hypertensive patients whose cardiovascular response to exercise was evaluated before and during methyldopa therapy, "...methyldopa significantly reduced the rise in systolic pressure during the build-up ($P<0.01$) and subjective maximal stages ($P<0.05$) as well as at all phases of recovery ($P<0.01$)." Moreover, "The total duration of exercise (an index of work capacity) was unchanged with...methyldopa."[3]

Such findings can be of importance to active hypertensive patients such as the athletic individual or the person whose work requires substantial physical effort. For these and many other hypertensive patients, ALDOMET represents a logical therapeutic choice.

With ALDOMET, exercise hypotension rarely occurs. Sedation, usually transient, may occur during the initial period of therapy or whenever the dose is increased. Headache, asthenia, or weakness may be noted as early and transient symptoms.

ALDOMET® offers many (METHYLDOPA|MSD) other important features:

- Highly effective in all degrees of hypertension.
- Existing cardiac output is usually maintained.
- Renal blood flow is usually maintained.
- Has documented long-term efficacy.
- Significant adverse effects have been infrequent and the agent is usually well tolerated.



ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders. It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed.

1. Yasky J, Carosella C, Costa O: Diagnosis of arterial hypertension by means of a graduated ergometric test, in Zanchetti A (ed): ALDOMET® (Methyldopa | MSD) in Worldwide Clinical Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 56-63.
2. Mancia G, Ferrari A, Gregorini G, et al: Effects of treatment with methyldopa on basal hemodynamics and on neural circulatory control, in Zanchetti A (ed): ALDOMET® (Methyldopa | MSD) in Worldwide Clinical Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 27-39.
3. Lee WR, Fox LM, Slotkoff LM: Effects of antihypertensive therapy on cardiovascular response to exercise. Am J Cardiol 44:325-328, 1979.

For hypertension—

ALDOMET® The most prescribed nondiuretic antihypertensive in the U.S. today
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TABLETS: 500 mg, 250 mg, and 125 mg
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For a brief summary of prescribing information, please see following page.
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For hypertension—

ALDOMET®
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The most prescribed nondiuretic antihypertensive in the U.S. today

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: *Central nervous system:* Sedation, headache, asthenia or weakness, usually early and transient; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.)

Gastrointestinal: Nausea, vomiting, distention, constipation, flatus, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundice, liver disorders.

Hematologic: Positive Coombs test, hemolytic anemia. Leukopenia, granulocytopenia, thrombocytopenia. Positive tests for antinuclear antibody, LE cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like syndrome, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited to 500 mg daily when given with antihypertensives other than thiazides. Tolerance may occur, usually between second and third months of therapy; increased dosage or adding a diuretic frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 mg methyldopa each, in bottles of 100; Tablets, containing 250 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 1000; Tablets, containing 500 mg methyldopa each, in single-unit packages of 100 and bottles of 100 and 500.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486

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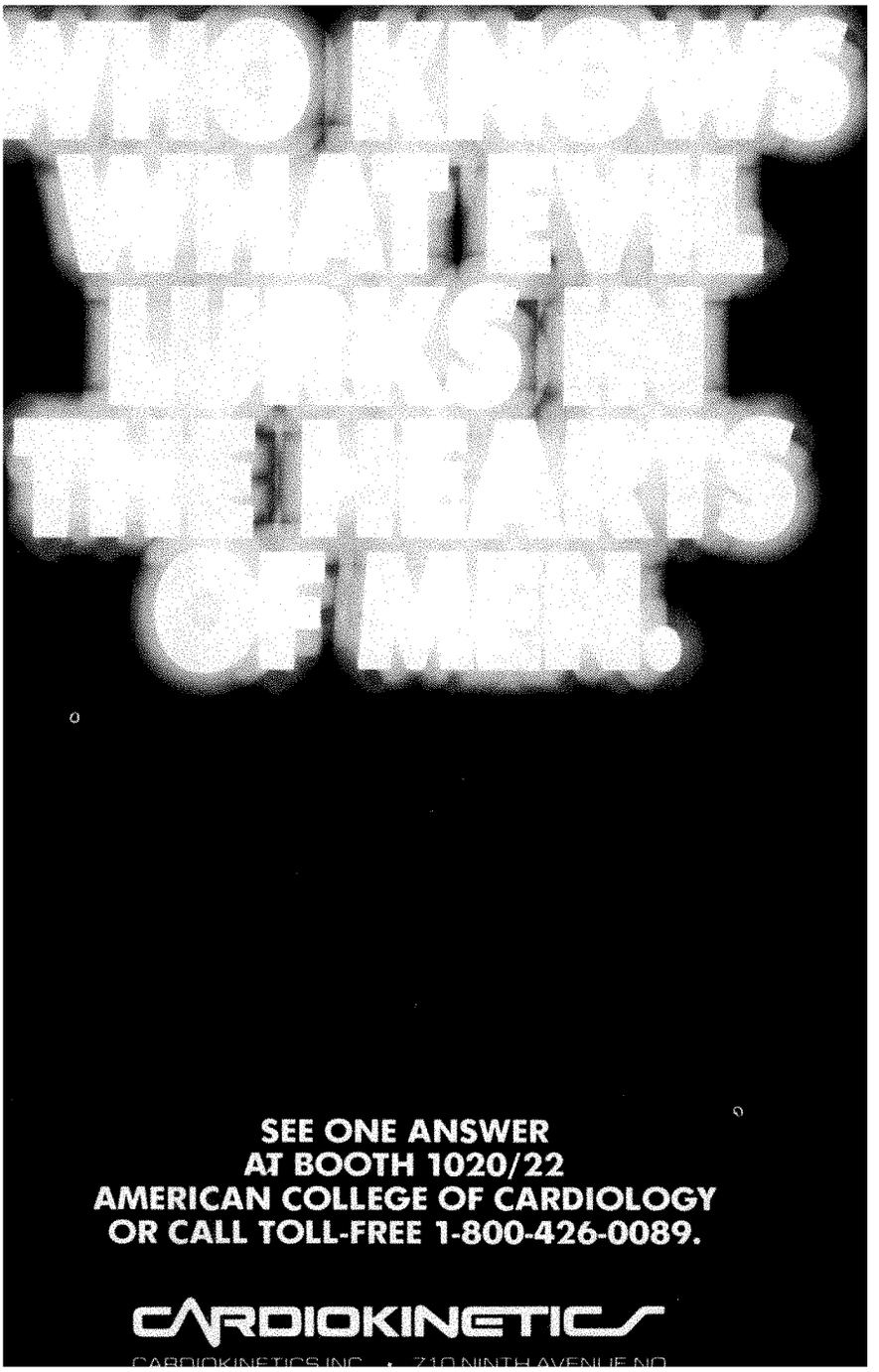

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FEBRUARY 1981 • VOLUME 47 • NUMBER 2 (IN TWO PARTS)

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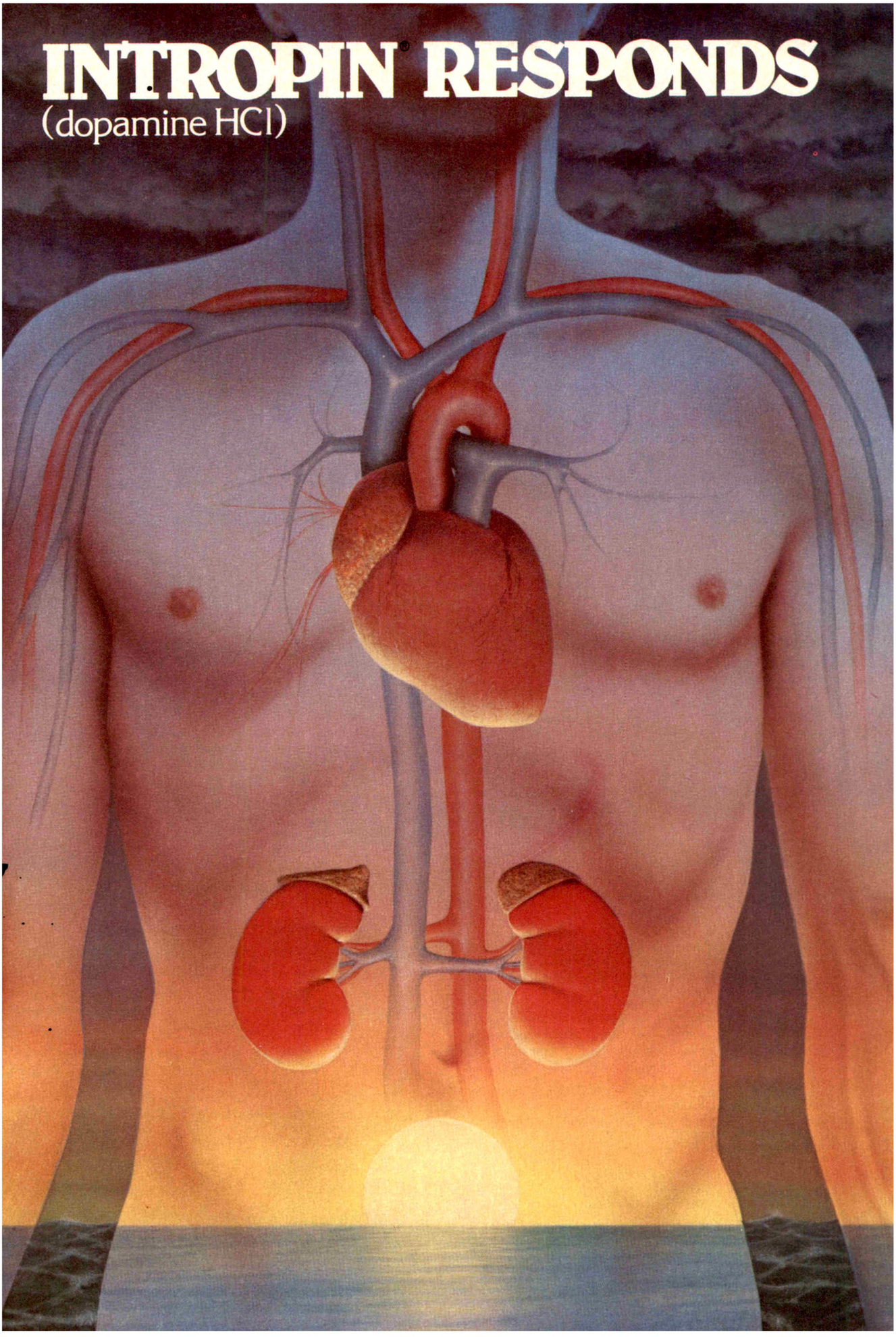
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- open heart surgery
- renal failure
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

DESCRIPTION: INTROPIN (dopamine HCl) is 3, 4-dihydroxyphenethylamine hydrochloride, a naturally occurring biochemical-cathecholamine precursor of norepinephrine. Intropin is a clear, aqueous additive solution for intravenous infusion after dilution.

INDICATIONS: For the correction of hemodynamic imbalances present in the shock syndrome due to myocardial infarctions, trauma, endotoxic septicemia, open heart surgery, renal failure, and chronic cardiac decompensation as in congestive failure.

Poor Perfusion of Vital Organs – Urine flow appears to be one of the better diagnostic signs by which adequacy of vital organ perfusion can be monitored. The physician should also observe the patient for signs of reversal of confusion or comatose condition. Loss of pallor, increase in toe temperature and/or adequacy of nail bed capillary filling may also be used as indices of adequate dosage. Note that at doses above those optimal for the individual patient, urine flow may decrease, necessitating reduction of dosage. Concurrent administration of INTROPIN and diuretic agents may produce a potentiating effect.

Low Cardiac Output – Increased cardiac output is related to the direct inotropic effect of INTROPIN on the myocardium. Increased cardiac output at low or moderate doses has been associated with either static or decreased systemic vascular resistance (SVR) and appears to be related to a favorable prognosis. Increase in cardiac output produced by INTROPIN is not associated with substantial decreases in SVR as may occur with isoproterenol.

Hypotension – Hypotension due to inadequate cardiac output can be managed by administration of low to moderate doses of INTROPIN, which have little effect on SVR. At high therapeutic doses, the drug's alpha adrenergic activity becomes more prominent and thus may correct hypotension due to diminished SVR. Administration should be considered as soon as a definite trend toward decreased systolic and diastolic pressure becomes evident.

CONTRAINDICATIONS: INTROPIN should not be used in patients with pheochromocytoma.

WARNINGS: INTROPIN should not be administered in the presence of uncorrected tachyarrhythmias or ventricular fibrillation. INTROPIN should not be added to any alkaline diluent solution since the drug is inactivated in alkaline solutions. Patients who have been treated with monamine oxidase (MAO) inhibitors prior to the administration of INTROPIN will require substantially reduced dosage (1/10 the usual starting dose).

Usage in Pregnancy – INTROPIN may be used in pregnant patients when, in the judgment of the physician, the expected benefits outweigh the potential risk to the fetus.

Usage in Children – The safety and efficacy of INTROPIN for pediatric use has not been established.

PRECAUTIONS: Avoid Hypovolemia – Prior to treatment with INTROPIN, hypovolemia should be fully corrected, if possible, with either whole blood or plasma as indicated.

Decreased Pulse Pressure – If a disproportionate rise in the diastolic pressure (i.e. a marked decrease in the pulse pressure) is observed in patients receiving INTROPIN, the infusion rate should be decreased and the patient observed carefully for further evidence of predominant vasoconstrictor activity, unless such an effect is desired.

Extravasation – INTROPIN should be infused into a large vein whenever possible to prevent the possibility of extravasation into tissue adjacent to the infusion site which may cause necrosis and sloughing of surrounding tissue. Large veins of the antecubital fossa are preferred to veins in the dorsum of the hand or ankle.

IMPORTANT – Antidote for Peripheral Ischemia: To prevent sloughing and necrosis in ischemic areas, the area should be infiltrated as soon as possible with 10 to 15 ml of saline solution containing from 5 to 10 mg of Regitine* (brand of phentolamine), an adrenergic blocking agent. A syringe with a fine hypodermic needle should be used, and the solution liberally infiltrated throughout the ischemic area. Sympathetic blockade with phentolamine causes immediate and conspicuous local hyperemic changes if the area is infiltrated within 12 hours. Therefore, *phentolamine should be given as soon as possible* after the extravasation is noted.

Avoid Cyclopropane or Halogenated Hydrocarbon Anesthetics – Because of the theoretical arrhythmogenic potential of these agents and the known increase in cardiac autonomic irritability which may sensitize the myocardium, INTROPIN should be used with EXTREME CAUTION in patients inhaling such anesthetics.

Careful Monitoring Required – As in the case of any adrenergic agent, infusion of INTROPIN should be accompanied by close monitoring of urine flow, cardiac output and blood pressure.

ADVERSE REACTIONS: The most frequent include ectopic beats, nausea, vomiting, tachycardia, anginal pain, palpitation, dyspnea, headache, hypotension, and vasoconstriction. Others reported infrequently are aberrant conduction, bradycardia, piloerection, widened QRS complex, azotemia, and elevated blood pressure.

WARNING: This is a potent drug – must be diluted before administration to patient.

OVERDOSAGE: In case of accidental overdosage, as evidenced by excessive blood pressure elevation, reduce rate of administration or temporarily discontinue INTROPIN until patient's condition stabilizes. Since the drug's duration of action is quite short, no additional remedial measures are usually necessary. If these measures fail to stabilize the patient's condition, use of the short-acting alpha adrenergic blocking agent, phentolamine, should be considered.

HOW SUPPLIED:
– 200 mg (5 ml containing 40 mg dopamine HCl per ml). NDC 0094-0040-05 – Ampul. NDC 0094-0040-06 – Single-dose vial (color coded white). NDC 0094-0040-07 – RAP-ADD® Additive Syringe (color coded white).
– 400 mg (5 ml containing 80 mg dopamine HCl per ml). NDC 0094-0046-06 – Single-dose vial (color coded green). NDC 0094-0046-07 – RAP-ADD® Additive Syringe (color coded green).

CAUTION: Federal law prohibits dispensing without a prescription. Full directions for use should be read before administering or prescribing.
November 1980

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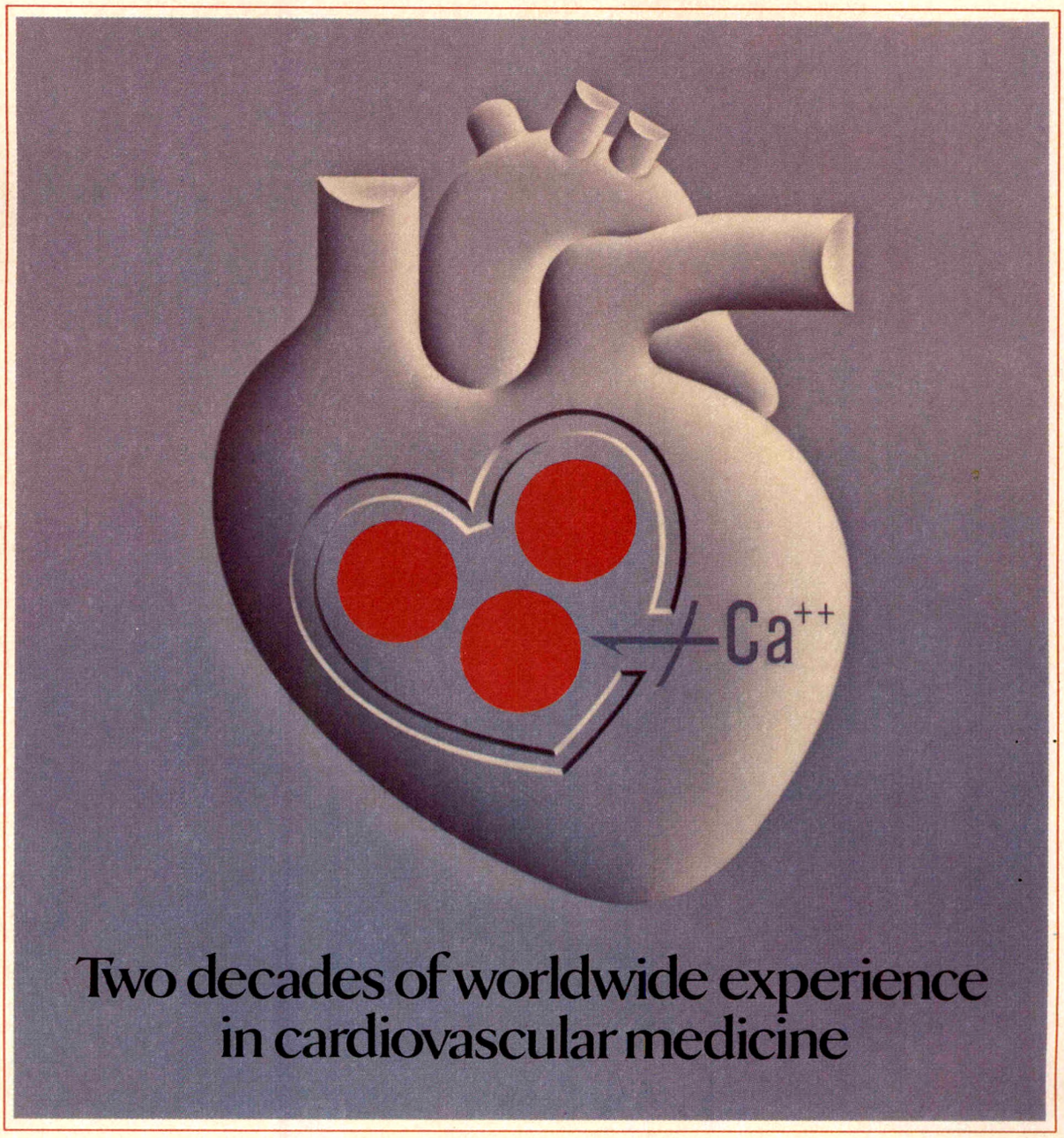

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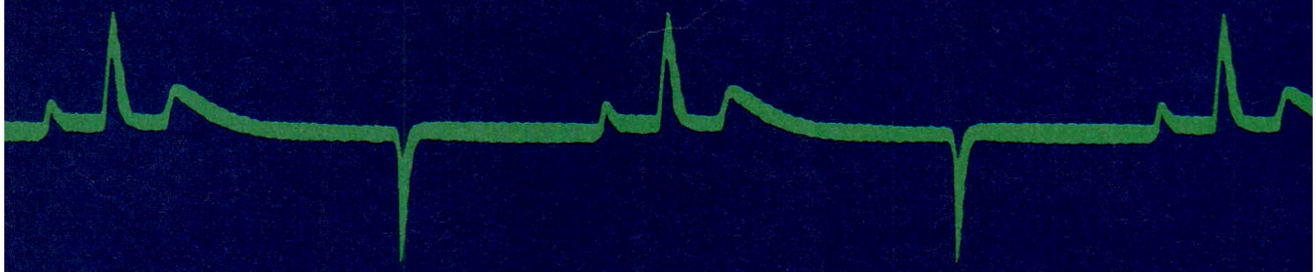

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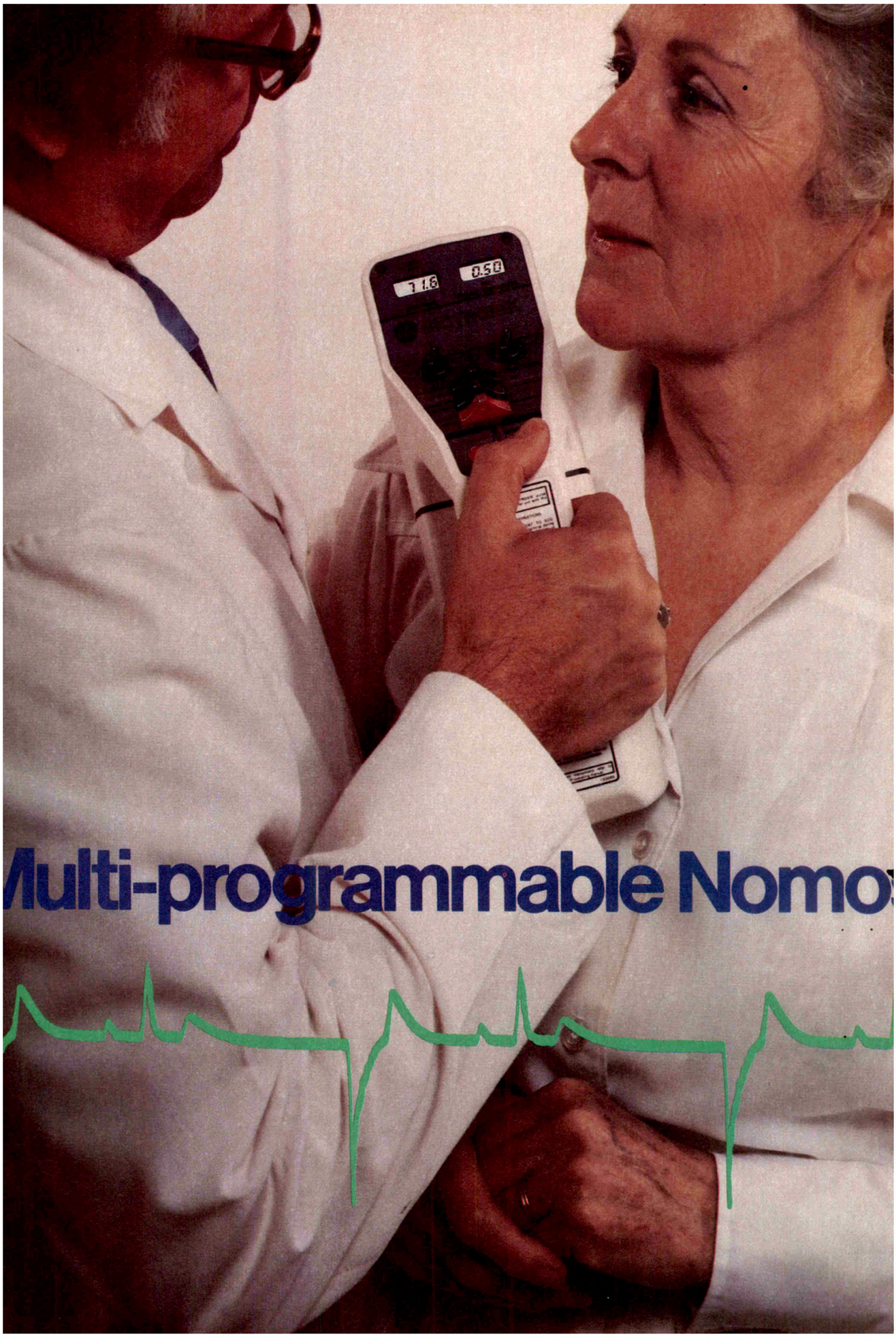
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The following reference style should be used when submitting manuscripts for publication in *The American Journal of Cardiology:*

1. Type all references in duplicate; double-space.
2. Number the references in the order in which they are referred to in the text.
3. Provide concluding page numbers for all journal references and specific page numbers for all book references. Indicate all abstracts by the abbreviation (abstr).
4. Follow the general arrangement and styles for abbreviations and punctuation shown below:

For periodicals, follow INDEX MEDICUS, listing *all* authors (if there are 7 or more, list only 3 and add et al.):

31. Vismara LA, Vera Z, Miller RR, Mason DT. Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 1977;39:1027–34.

For chapter in book:

28. Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. Heart Disease in Infants, Children and Adolescents. Baltimore: Williams & Wilkins, 1968: 134–9.

For books (personal author or authors):

36. Berne E. Principles of Group Treatment. New York: Oxford University Press, 1966:27.

For further information, see page 342.

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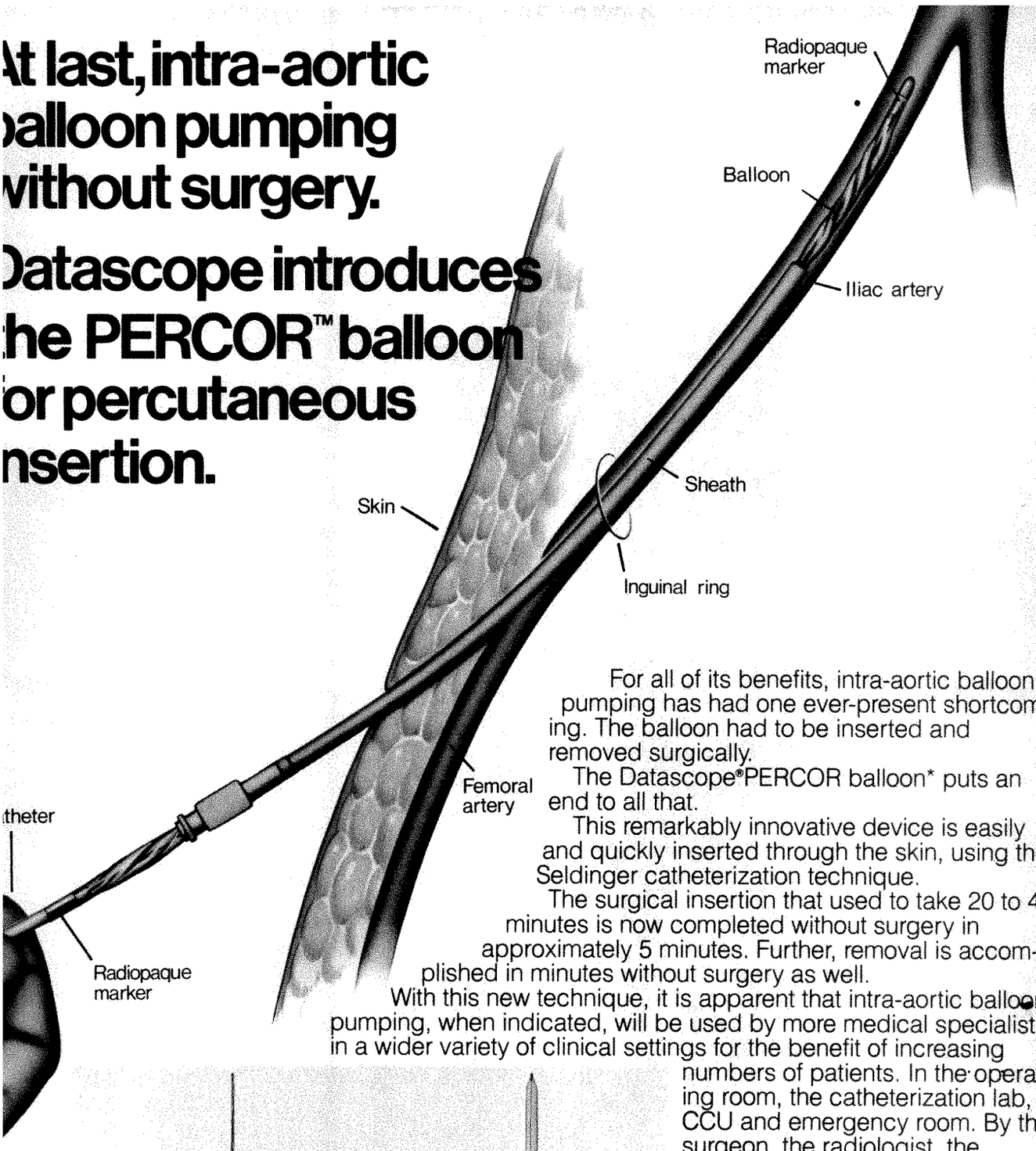

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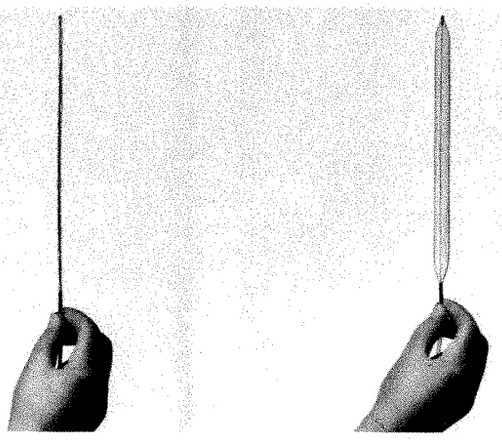

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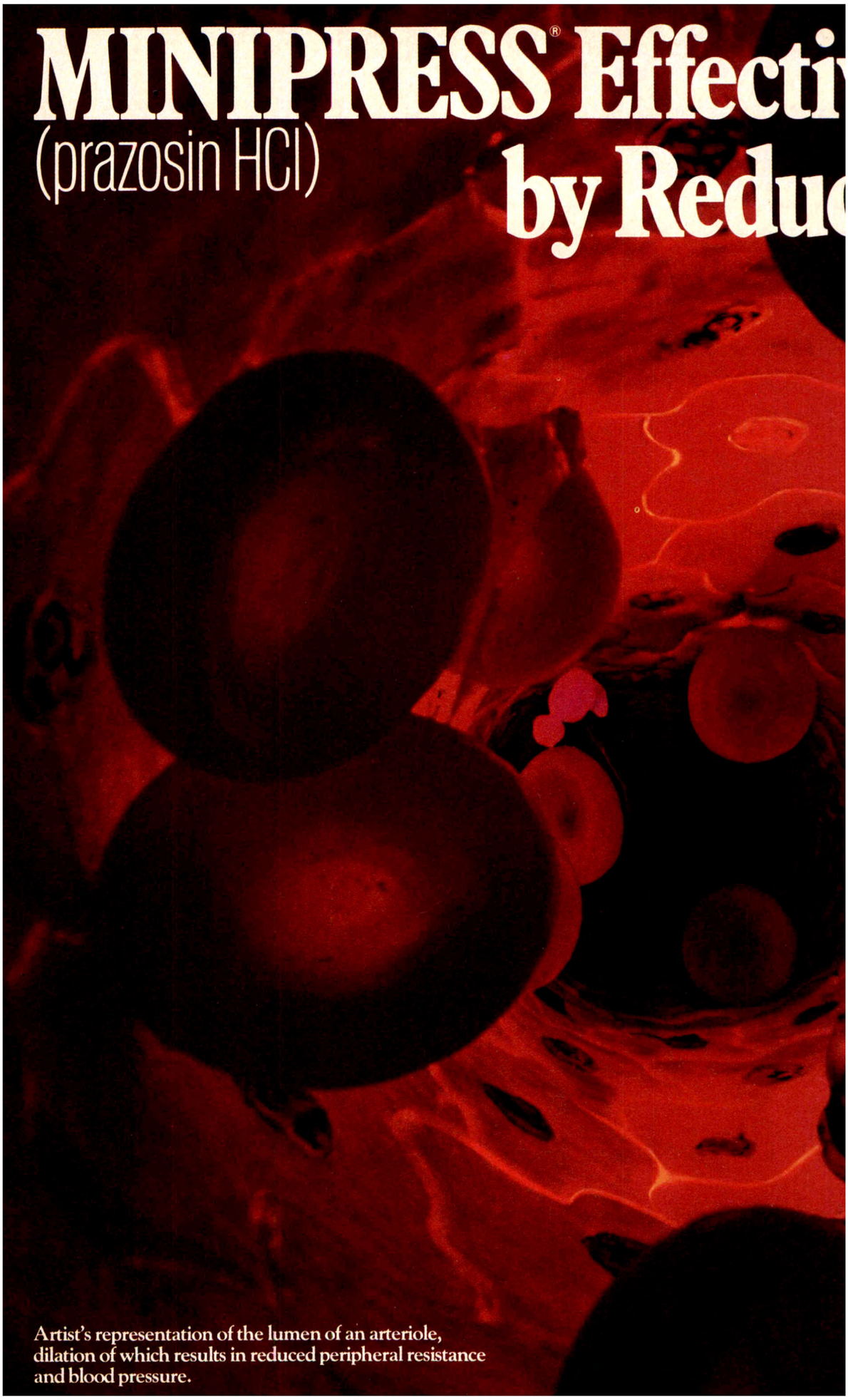
Clinical reference: *Preliminary Clinical Experience With Percutaneous Intra-Aortic Balloon Pumping (IABP),* V. A. Subramanian, Jonathan Goldstein, Thomas A. Sos, John C. McCabe, Eddie Hoover & William A. Gay, Jr., New York Hospital, New York, NY. Abstract published in CIRCULATION, Part II,


MINIPRESS® Effecti
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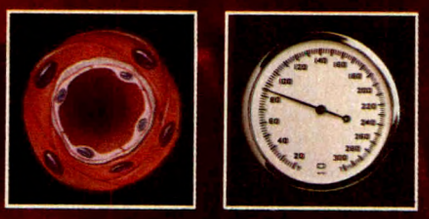
Artist's representation of the lumen of an arteriole,
dilation of which results in reduced peripheral resistance
and blood pressure.

Controls Hypertension
Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
- MINIPRESS Reduces Total Peripheral Resistance
- MINIPRESS Does Not Reduce Cardiac Index

...and Maintains These Effects Over the Long Term

Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen[1]

Rest Exercise

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(prazosin HCl)

Capsules 1 mg, 2 mg, 5 mg

Please see Brief Summary on last page.

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MINIPRESS®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

- **Effectively lowers elevated blood pressure by reducing peripheral resistance.**
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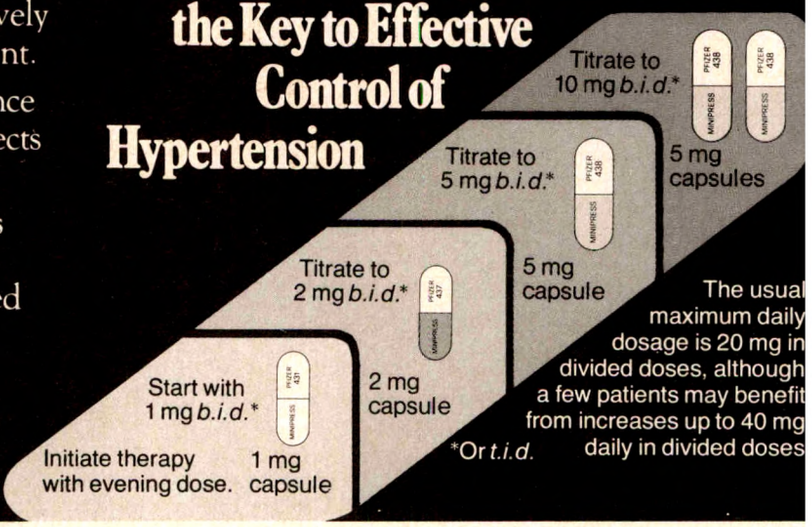
- **Not a CNS agent** so patients experience few of the troublesome CNS side effects that impair their quality of life.
- **Cardiovascular response to exercise is preserved** so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- **A small percentage of patients** have experienced orthostatic hypotension and syncope.

B.I.D. Dosage Titration... the Key to Effective Control of Hypertension



BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.

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Abstracts of Papers to Be Presented at the 30th Annual Scientific Session of the American College of Cardiology San Francisco, California, March 15–19, 1981

This year, a record number of abstracts (original contributions), 2,300, were submitted for evaluation. Each was graded by seven recognized authorities in a special area of interest. Acceptance for presentation was based on the relative grade ranking in each of these 17 categories.

Meeting space restrictions limited the total number of original contributions that could be presented to 18 percent of the number submitted, or 442 abstracts. This, however, represents the largest number of abstracts accepted for presentation at any American College of Cardiology Annual Scientific Session. Many excellent contributions could not be included in the program because of the space limitations. We regret any disappointment this has undoubtedly caused many authors.

Emilio R. Giuliani, MD, FACC
Dwight C. McGoon, MD, FACC
Co-Chairmen, 1981 Scientific Session
Program Committee

MONDAY, MARCH 16, 1981
AM
PHARMACOLOGY: VASODILATORS—NEW CONCEPTS
10:30–12:00

DIRECT EFFECTS OF PRAZOSIN ON THE CANINE SINUS NODE. Kerry M. Schwartz, M.D., Ferdinand Urthaler, M.D., and Thomas N. James, M.D., FACC. University of Alabama in Birmingham, Birmingham, Alabama.

Prazosin differs from most blockers of post-synaptic alpha adrenoceptors by rarely causing the expected reflex tachycardia. Selective perfusion (2 ml) of the sinus node artery (SNA) of 16 anesthetized dogs was utilized to assess the direct and indirect chronotropic effects of prazosin (PRZ). Concentrations of 1.0, 10, 50, and 100 µg/ml produced cumulative, dose-related reductions in mean sinus rate (SR) of 4.4 ± 2; 10.3 ± 6; 15 ± 9; and 27 ± 15 beats/min respectively ($p < .0001$). Intranodal PRZ (1.0-100 µg/ml) did not significantly alter the sinus node response to intranodal norepinephrine (NE) (.05 and .10 µg/ml) given via the SNA (n=6). SR acceleration (stimulus frequency response curve) after right stellate stimulation (n=6) was also not influenced by PRZ (control % change at 8 Hz was 45 ± 17 vs PRZ 48 ± 17, 40 ± 19, 52 ± 14, 53 ± 14 for 1, 10, 50, 100 µg/ml doses respectively; control % at 16 Hz was 50 ± 19 vs PRZ 52 ± 20, 52 ± 23, 57 ± 15, 55 ± 16; control % at 32 Hz was 52 ± 20 vs 57 ± 23, 61 ± 23 and 58 ± 18 respectively). Response to vagal stimulation (n=8) was also not affected by prior administration of PRZ in SNA (control % slowing at 8 Hz was 39 ± 12 vs PRZ 40 ± 14, 39 ± 13, 37 ± 14 and 35 ± 14; control at 16 Hz was 58 ± 9 vs PRZ 59 ± 11, 60 ± 11, 57 ± 16 and 47 ± 20, for 1, 10, 50, 100 µg/ml respectively). Conclusion: Prazosin exerts a direct negative chronotropic effect without exerting any significant influence on the neurohumoral autonomic control of the sinus node.

MECHANISM OF TRANSIENT PRAZOSIN HEMODYNAMIC "TACHYPHYLAXIS" IN HEART FAILURE: ACUTE, SUBACUTE AND LATE SERIAL EVALUATION OF ALPHA RECEPTOR RESPONSES WITH PHENYLEPHRINE BY CARDIAC CATHETERIZATION DURING PROLONGED ORAL PRAZOSIN THERAPY.
Dean T. Mason, MD, FACC; Najam A. Awan, MD, FACC; Kathleen E. Needham, BS; Mark Evenson, BS; Ezra A. Amsterdam, MD, FACC, University of California, Davis.

The mechanism of subacute hemodynamic "tachyphylaxis" (TX) to oral prazosin (PZ) during long-term ambulatory therapy of chronic congestive heart failure (CHF) is unknown. Accordingly, constant dose (20 ug/min) phenylephrine (PH) was serially infused during cardiac catheterization before and after oral prazosin on Day 1, Day 4, and Day 30 of continuous oral PZ (5 mgm q.i.d.) therapy in 9 patients with severe CHF. Measurements: MBP=mean blood pressure, mmHg; LVFP=left ventricular filling pressure, mmHg; CI=cardiac index, L/min/M^2. Control (C) vs drug: **=$p < 0.01$, + = $p < 0.001$. PZ vs PZ+PH: *=$p < 0.05$.

	DAY 1			DAY 4			DAY 30		
	MBP	LVFP	CI	MBP	LVFP	CI	MBP	LVFP	CI
C	79	22	2.2	79	22	2.4	81	22	2.1
PH	99+	31+	1.9**	89+	29**	2.3	91+	26**	2.2
PZ	71+	17+	2.6+	78	21	2.7	74+	17**	2.8+
PZ+PH	74*	19*	2.6	84*	25*	2.5	77	19*	2.8

Therefore PH raised BP and worsened cardiac function acutely, subacutely and on Day 30. Moreover while initial marked PZ beneficial effects were attenuated by Day 4, PZ vasodilator effects were fully restored by Day 30. Concomitantly initial post-PZ marked PH stimulation block was attenuated by Day 4 and recurred by Day 30. Thus the mechanism of PZ "tachyphylaxis" is altered PZ-alpha receptor interaction while alpha receptor integrity is maintained. Moreover this modified prazosin-alpha receptor response is transient and disappears during sustained oral PZ therapy of severe congestive heart failure.

ASSESSMENT OF PRAZOSIN ALPHA RECEPTOR BLOCKADE WITH PHENTOLAMINE: ACUTE, SUBACUTE AND LATE HEMODYNAMIC EVALUATION DURING SUSTAINED BENEFICIAL VASODILATOR THERAPY IN CONGESTIVE HEART FAILURE

Mark K. Evenson, BS; Najam A. Awan, MD, FACC; Kathleen E. Needham, BS; and Dean T. Mason, MD, FACC, University of California, Davis.

The mechanism of transient subacute hemodynamic blunting of prazosin (PZ) effects in therapy of chronic congestive heart failure (CHF) is uncertain. Therefore we evaluated the efficacy of PZ alpha receptor (AR) blockade by phentolamine (PT, 1.3 mg/min) acutely (Day 1), subacutely (Day 4) and chronically (Day 30) during continuous unaltered PZ (5 mg qid) therapy. Measurements: mean blood pressure (MBP), mmHg; left ventricular filling pressure (LVFP), mmHg; cardiac index (CI) L/min/M^2. Drug vs control (C): *=p<0.05, **=p<0.01, +=p<0.001, PZ+PT vs PZ: o=p<0.01.

	DAY 1			DAY 4			DAY 30		
	MBP	LVFP	CI	MBP	LVFP	CI	MBP	LVFP	CI
C	85	22	2.1	83	25	2.3	83	23	2.0
PT	72+	16*	2.4*	75+	23*	2.6+	79*	19*	2.5*
PZ	71+	17+	2.6+	82	23	2.5	74+	17**	2.8+
PZ+PT	70*^{o}	16+	2.5+	78*^{o}	21*^{o}	2.7*^{o}	78*	19**	2.6++

Accordingly, while the beneficial vasodilator effects of PT on cardiac function are blunted by salutary acute PZ responses on Day 1, during transient subacute PZ "tachyphylaxis" (Day 4) phentolamine responses are unaltered by PZ. Further with continuous 30 day oral PZ therapy of CHF, the spontaneous return of beneficial PZ effects causes restoration of post-PZ phentolamine block on Day 30. Thus the mechanism of transient PZ "tachyphylaxis" is temporarily modified PZ-AR relation while the alpha receptor itself remains responsive to vasodilation. Importantly, transient subacute blunting of PZ hemodynamic effects by modified PZ-AR interaction does not effect successful long term therapy of CHF with prazosin.

MAXIMAL IMPROVEMENT IN VENTRICULAR PERFORMANCE DURING REST AND EXERCISE IN CHRONIC SEVERE CARDIAC FAILURE BY COMBINED INOTROPIC AND VASODILATOR THERAPY COMPARED TO EITHER MODALITY ALONE.

Stephen P. Rosenfeld, M.D., FACC, M. Sheila Carney, R.N., Alan D. Waggoner, RDMS, Lawrence R. Poliner, M.D., FACC, Miguel A. Quinones, M.D., FACC, Craig M. Pratt, M.D., FACC, Richard R. Miller, M.D., FACC, Baylor College of Medicine, Houston, Texas.

Acutely, combined positive inotropic and vasodilator (Vas) therapy is superior to either individually in LV failure (F); however, the comparative effects chronically and at both rest (Rst) and exercise (Ex) are unknown. We compared digitalis (Dig) (serum level 1.3±.1 ng/ml) plus maximal Vas [prazosin (n=4) or hydralazine + nitrate (n=14)] and diuretic (DT) vs Dig+DT vs Vas+DT vs DT alone in 18 patients with extreme LVF [mean LV ejection fraction (EF) 16±7 (SD) % (all <30%), (nine ischemic)] by Rst and Ex radionuclide EF, treadmill (T) tolerance (sec), echophono and 48 hr ECG.

	Rst-EF	Ex-EF	T-Ex	EDD	PEP/LVET	PVC/hr
DT	16±2	20±3	362±40	6.5±.8	.59±.06	73±27
Dig	21±2†	21±3	336±61	6.6±.8	.50±.03**	88±32
Vas	19±3*	23±5	395±50	6.5±.8	.57±.04	82±24
Dig+Vas	23±3**	26±3†Ψ	409±70	6.5±.7	.53±.05	111±67

EDD=end-diastolic dimension (cm). *=p<.05 vs DT; †=p<.02 vs DT; **=p<.05 vs DT and Vas; Ψ=p<.05 vs Dig. Left atrial size was similar (p=ns) in each group. With Dig, Rst heart rate ↓ and Rst + Ex BP ↑ (p<.02) vs DT and Vas. Dig+Vas had lower (p<.02) PVC severity score vs Vas although PVC/hr were similar (p=ns). Thus, in extreme LVF neither Dig nor Vas separately increase Ex-EF vs DT alone. Dig+Vas combined ↑ Rst and Ex-EF vs DT, ↑ Rst-EF vs Vas and ↑ Ex-EF vs Dig (both p<.05). These data provide objective rationale for the chronic use of combined inotropic and vasodilator therapy in extreme LV dysfunction.

HEMODYNAMIC EFFECTS OF HYDRALAZINE IN PATIENTS WITH ISOLATED RIGHT VENTRICULAR FAILURE

Franklin Handel, MD; Robert H. Peter, MD, FACC; Lewis J. Rubin, MD, Duke University Medical Center, Durham, N.C.

Fifteen patients with isolated right ventricular failure secondary to pulmonary hypertension were evaluated for response to oral hydralazine(H). Three had idiopathic pulmonary hypertension, three closed ASDs, two closed VSDs, three COPD, two chronic pulmonary emboli, and two pulmonary fibrosis. All patients underwent right heart catheterization; none had LV dysfunction. Mean systemic pressure(MSP), mean pulmonary artery pressure(MPP), right atrial pressure(RA), right ventricular end diastolic pressure(RVEDP), pulmonary capillary wedge pressure(PCWP), cardiac index(CI), arteriovenous O_2 difference(AVO_2), heart rate(HR), total pulmonary resistance(TPR), and pulmonary arteriolar resistance(PAR) were measured for all patients at baseline(C). Rest studies (H) were then repeated after eight doses of 50 mg H orally q6h.

	MSP	MPP	RA	RVEDP	PCWP	CI	AVO_2	HR	TPR	PAR
R	99	62	15	17	9	2.2	8.0	87	19	12
Mean	±29	±23	±7	±5	±3	±.6	±2.3	±15	±14	±6
+S.D.	87	57	11	11	8	3.2	6.2	95	13	7
H	±23	±21	±6	±5	±3	±1.1	±2.0	±13	±11	±4
p	**	*	**	***	*	***	***	NS	***	***

p = *<.05; **<.01; ***<.001 by Student's two-tailed t test.

The above data suggests that oral hydralazine significantly increases cardiac output, lowers right ventricular end diastolic pressure, and lowers pulmonary vascular resistance in patients with right ventricular failure secondary to pulmonary hypertension.

INHIBITION OF NITROGLYCERIN EFFECT IN HUMANS BY SUPPRESSION OF PROSTAGLANDIN E

James Van Dusen, D.O.; Stephen J. Fischl, M.D., FACC; Overlook Hospital, Summit, New Jersey

10 healthy volunteers were studied supine using a mercury-in-rubber strain gauge plethysomograph and indwelling venous pressure cannula in the forearm. Volume-pressure characteristics of the forearm veins were determined using 15 second automatic cuff occlusions of the limb. Percent change of forearm volume (%ΔV) and change of venous compliance (C) were measured at rest and following 0.1 mg. sublingual nitroglycerin (NTG). Indomethacin (I) 150 mg. per day was administered to each volunteer for one week and the measurements were repeated.

The expected increments in limb volume and C during control cuff occlusions were 28% and 26% higher, respectively, after NTG. After I therapy and cuff occlusion, increments in limb volume and C were 25% and 39%, respectively, lower than control. While on I, mean increments in limb volume and C did not change significantly following NTG.

	15 second occlusion @ 40 mmHg			
	%Δ in volume		C(%Δ in volume/mmHg)	
Control	.32 ± .04	(p<.05)	.023 ± .007	(p<.05)
NTG	.41 ± .05		.029 ± .009	
I-Control	.24 ± .04		.014 ± .004	
I & NTG	.22 ± .04		.013 ± .013	

Therefore, augmentation of volume and compliance of the peripheral vasculature by NTG is inhibited by prior administration of I, presumably by suppression of prostaglandin E synthesis. This supports the concept that prostaglandins may be important mediators for the action of NTG in humans. Perhaps, patients receiving nitrates should be observed for this possible drug interaction with prostaglandin-inhibiting drugs.

MONDAY, MARCH 16, 1981
AM
VENTRICLES I: TACHYCARDIA AND FIBRILLATION
10:30-12:00

SIMULTANEOUS OPERATION OF MULTIPLE REENTRANT CIRCUITS DURING UNIFORM VENTRICULAR TACHYCARDIA

Benjamin J. Scherlag, PhD, FACC, Glenn Kabell, PhD, Johannes Brachmann, MD, Lura A. Harrison, PhD; Ralph Lazzara, MD, FACC. Veterans Administration Medical Center, University of Oklahoma, Oklahoma City, Oklahoma.

The association of reentrant ventricular tachycardia (VT) and continuous electrical activity (CEA) from the epicardium (epi) of the infarcted dog heart has been previously documented. In 14 dogs with 4 day old anterior wall myocardial infarction ECG leads, His bundle electrograms, epi and endocardial (endo) electrograms were recorded. Ventricular pacing, 3 beats at 300-420/min, was used to induce sustained VT with uniform QRS morphology in all 14 dogs either before (7 dogs) or after (7 dogs) administration of 2-6 mg/kg lidocaine. In 8 CEA was recorded only in the epi overlying the infarct during sustained VT. During VT in 2 dogs CEA was seen in both epi and endo recordings. However, the reentrant loop in the endo controlled the VT since CEA in the epi was intermittent but the endo CEA was constant and quantitatively linked to the R-R cycle length. In 3 dogs, during sustained VT, CEA in endo or epi coexisted with evidence of bundle branch macro-reentry in which the His and left bundle potentials were recorded between the QRS complexes. The underlying macro-reentry was unmasked when the CEA abruptly terminated. In 2 dogs, the epi CEA and QRS form during VT was replaced by an endo CEA pattern and different QRS form after lidocaine. With a higher dose of lidocaine, the induced VT showed portions of both epi CEA and endo CEA. The QRS form reflected the latter VT. We conclude that multiple reentrant loops, operating simultaneously, can be identified during uniform VT. The VT may be dominated by one circuit or may result from fusion of two circuits.

COMPARATIVE EFFECTS OF CYCLE LENGTH ON VENTRICULAR REFRACTORINESS OF NORMAL AND CHRONICALLY INFARCTED MYOCARDIUM

Eric L. Michelson, MD, FACC, Masahito Naito, MD, Joseph F. Spear, PhD, FACC, Daniel David, MD, E. Neil Moore, DVM, PhD, FACC. Lankenau Hospital and the University of Pennsylvania, Philadelphia, Pennsylvania

Although refractory periods(RP) measured in normal(N) ventricular muscle shorten when the pacing cycle length(CL) is decreased, the response of chronically infarcted(I), myocardium to CL changes is not known. This was evaluated in 13 dogs susceptible to pacing-induced sustained ventricular tachyarrhythmias(VT) studied $\geq$ 4 days after 2-stage coronary artery occlusion and reperfusion. Strength-interval curves were constructed at 24 N and 40 I intramyocardial sites during ventricular pacing at CL 500 msec and CL 300 msec using unipolar cathodal stimulation. Mean RPs measured using twice diastolic excitability threshold current(2x ET),5x ET, and 10 milliamps (ma) were compared:

Normal (msec)	RP(2x ET)	RP(5x ET)	RP(10 ma)
CL 500	195	189	178
CL 300	167	161	149
Infarct (msec)			
CL 500	239	227	218
CL 300	200	187	177

Thus, by decreasing the CL, mean RPs shortened to a similar extent at I($\geq$ 39 msec) and N($\geq$ 28 msec, p=NS) sites at each of these current intensities. However, even at shorter CLs, RPs at I sites remained markedly prolonged compared to N sites(difference $\geq$ 26 msec at CL 300, $p<0.001$). These findings suggest first, that in clinical electrophysiologic studies, one must consider the possible differences between N and I sites when interpreting the effects of various interventions on refractoriness; and second, that decreasing the CL may be an important means to facilitate initiation of those VTs requiring critically short coupling intervals, especially when pacing from areas of chronic infarction.

THE REPETITIVE EXTRASYSTOLE AS AN INDEX OF VULNERABILITY TO VENTRICULAR FIBRILLATION DURING MYOCARDIAL ISCHEMIA

Peter R. Kowey, MD; Richard L. Verrier, PhD, FACC; Bernard Lown, MD, FACC, Harvard School of Public Health and Harvard Medical School, Boston, MA.

The repetitive extrasystole threshold (RET) is a useful measure of vulnerability to ventricular fibrillation in the normal canine heart using the single stimulus technique. Whether this relationship obtains during graded degrees of myocardial ischemia has not been explored. In 13 chloralose-anesthetized dogs, left circumflex coronary blood flow (CBF) was decreased in a stepwise fashion using an externally-applied balloon occluder. There was a statistically significant correlation between the RET and ventricular fibrillation threshold (VFT) until coronary blood flow was reduced by 90% of control values ($r = .92$). With reductions of CBF greater than 90%, the RET/VFT ratio was disrupted.

CBF Reduction	RET (ma)	VFT (MA)	RET/VFT
Control	18 $\pm$ 1	30 $\pm$ 3	0.60
50%	13 $\pm$ 1*	22 $\pm$ 3*	0.59
75%	12 $\pm$ 1*	20 $\pm$ 3*	0.60
90%	14 $\pm$ 2*	16 $\pm$ 2*	0.88*

(*$P < 0.01$ compared with control)

Total coronary occlusion performed either abruptly or gradually (5 minutes) likewise increased the RET/VFT ratio. During total occlusion of one hour, the VFT recovered to control values within 15 minutes and the RET/VFT ratio was restored. We conclude that the elicitation of repetitive extrasystoles is a reliable index of vulnerability to VF which is not invalidated by near total occlusion of a major coronary vessel. It remains to be determined whether the disruption of the relationship is determined by the amount of ischemia produced or by other factors.

THE EFFECT OF INTERRUPTION OF COLLATERAL BLOOD FLOW ON CONDUCTION DELAY AND ARRHYTHMIAS DURING ACUTE MYOCARDIAL ISCHEMIA

David E. Euler, Ph.D., Charles E. Prood, M.A., E. Neil Moore, D.V.M., Ph.D., F.A.C.C. and Joseph F. Spear, Ph.D., F.A.C.C., University of Pennsylvania, Phila., Pa.

We studied the importance of collateral blood flow (CBF) on the genesis of epicardial conduction delay (ECD) and ventricular arrhythmias (VA) by comparing the electrophysiologic effects of coronary occlusion (CO) vs. coronary embolization (CE). In 23 open-chest anesthetized dogs, heart rate was held constant at 180/min and the proximal left anterior descending artery (LAD) was occluded for 10 minutes followed by 30 minutes of reperfusion. The LAD was then ligated and a rapidly hardening (10-20 sec) vinyl latex was injected just below the ligature. The latex filled all vessels branching from the LAD down to a diameter of 20-30 u. The amount of ECD was measured during atrial rhythm at 6 bipolar electrode sites located within the distribution of the LAD. The maximal ECD during CO was 97 $\pm$ 48 msec (mean $\pm$ SD) while CE increased the delay to 203 $\pm$ 51 msec ($p < .001$). During CO, 6% of the electrograms showed delayed activation occurring beyond the T-wave of the ECG while 28% of the electrograms showed post T-wave activation following CE ($p < .001$). During CO, 8% of the electrograms demonstrated alternation while 58% showed alternation during CE ($p < .001$). CO evoked ventricular fibrillation in 25% of the animals while no animal fibrillated following CE ($p < .001$). The results indicate that interruption of CBF to the ischemic myocardium increases the severity of local conduction abnormalities while reducing the incidence of lethal arrhythmias. The interruption of CBF may decrease the susceptibility of the ventricles to fibrillate by converting unidirectional block to bidirectional block.

ELECTRICAL INSTABILITY AS A FUNCTION OF MYOCARDIAL INFARCTION SIZE

Beverly A. Jones Collins, MD, Randolph E. Patterson, MD, FACC, Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

The predisposing factors for post-infarction ventricular arrhythmias are ill-defined, and although indirect evidence supports the possibility that size of acute myocardial infarction is an important determining factor, no direct evidence exists. We therefore studied 13 conscious dogs 3 to 4 days after acute myocardial infarction was produced by closed chest coronary artery occlusion. The right ventricle was stimulated by a series of single, followed by double extrastimuli, scanning from end-diastole toward the T wave during right ventricle pacing. Abnormal responses included: repetitive ventricular responses (RVR), short runs of ventricular tachycardia (VT), sustained VT (SVT) and ventricular fibrillation (VF). An index of electrical instability was determined for each dog by the type of responses produced (score for VF>SVT>VT>RVR), the nature of the stimuli required to produce the responses (score for single>-double) and the time in diastole at which they could be elicited (score for late>early diastole). Myocardial infarction size was measured by post- mortem tetrazolium staining. Electrical instability correlated strongly with myocardial infarction size (r=.93). This is the first study utilizing direct measurement of myocardial infarction size to demonstrate that electrical instability several days post-AMI, as determined by electrical stimulation, is a function of myocardial infarction size.

MEOBENTINE SULFATE: ANTIARRHYTHMIC EFFICACY AND MECHANISM OF ACTION IN A CHRONIC CANINE MODEL OF MYOCARDIAL INFARCTION SUSCEPTIBLE TO VENTRICULAR TACHYARRHYTHMIAS

Eric L. Michelson, MD, FACC, Masahito Naito, MD, Daniel David, MD, E. Neil Moore, DVM, PhD, FACC, Leonard S. Dreifus, MD, FACC. Lankenau Hospital, Philadelphia, PA

The antiarrhythmic efficacy of meobentine sulfate(MBS), a non-neuronal blocking bethanidine derivative was evaluated in 6 open-chest pentobarbital-anesthesized dogs studied 4-6 days after 2-stage left anterior descending coronary artery occlusion and reperfusion. Prior to MBS, each dog was reproducibly susceptible to pacing-induced sustained ventricular fibrillation(VF,N=5 dogs)or tachycardia(VT, 1 dog). After intravenous infusion of 20 mg/kg MBS over 30 min, MBS demonstrated marked antiarrhythmic activity in each dog. In the 5 dogs with VF prior to MBS, VF re-initiation was prevented for a range of 5-12 hrs. In the one dog with VT prior to MBS,re-initiation of VT was prevented for 2hrs;VT then recurred at a slower rate until 6 hrs after drug infusion. This time course of antiarrhythmic activity paralleled the left ventricular tissue kinetics of MBS($T_{\frac{1}{2}}$ elimination=3 hrs) rather than its plasma concentration (α $T_{\frac{1}{2}}$ = 1.8 min, β $T_{\frac{1}{2}}$ = 90 min). Of note, MBS had no effect on the diastolic excitability threshold of either normal(N)or infarct(I)tissue at the time of its antiarrhythmic activity,but did prolong ventricular refractory periods(VRP)at both N(mean increase 25 $\pm$ 7(SD)msec at a paced cycle length of 300 msec,$p < 0.01$)and I sites(by 69 $\pm$ 23 msec, $p < 0.01$). Prolongations of VRPs at I sites were both more marked($p < 0.01$)and of longer duration (167 $\pm$ 71 min)than at N sites(120 $\pm$ 49 min,$p < 0.01$), and correlated with the time course of antiarrhythmic activity.Thus, MBS is an effective antiarrhythmic drug in this chronic model of inducible VT/VF and has a long duration of activity. Its mechanism of action appears to be related to myocardial drug uptake and prolongation of VRPs, particularly within areas of abnormal myocardium.

MONDAY, MARCH 16, 1981
AM
CARDIAC PACING
10:30-12:00

NON-INVASIVE SERIAL ELECTROPHYSIOLOGIC TESTING USING AN IMPLANTED PACEMAKER TO TRACK CHEST WALL STIMULI

Ross Fletcher, MD, FACC; John Keimel, MSEE, Lou Larca, MD; James Cox, MEEE; Albert Del Negro, MD; Robert Di Bianco, MD, FACC; Steve Singh, MD; VA Medical Center, Georgetown University, Washington, D.C.

A new technique for serial non-invasive electrophysiologic testing (EPT) was verified in 18 studies on 9 pts with an implanted multiprogrammable pacemaker * attached to ventricular (5pts) and atrial (4pts) leads. After programming ** the pacemaker to a triggered mode at outputs 2 times threshold, an external stimulator delivered premature impulses to the chest wall at outputs below patient perception thru electrode patches. External leads (6) and an esophageal lead determined responses.

The internal pacemaker tracked chest wall stimuli down to 220msec (the refractory period of the pacemaker). The effective refractory period of the ventricles (250$\pm$24msec) and atria (270$\pm$34msec) was longer than 220msec. Two ventricular pacemaker pts with clinical ventricular tachycardia had tachycardia induced with premature stimuli of 320msec and 330msec, and were reverted by tracking chest wall stimuli or programmed overdrive pacing. Three ventricular pacemaker pts without tachycardia had $\leq$ 2 repetitive beats following 1, 2 or 3 premature stimuli. Four atrial pacemaker pts had 6 supraventricular arrhythmias (4SVT, 2 atrial flutter) induced which were reverted by tracking chest wall stimuli (4) or rapid pacing (2). Repeat testing verified antiarrhythmic control after drug intervention in the 5/6 pts with arrhythmia.

Non-invasive serial EPT using permanent multiprogrammable pacemakers tracking chest wall stimuli is effective for inducing and reverting ventricular and atrial arrhytmias and in evaluating antiarrhythmic therapy.

* Medtronic, Inc. Spectrax ^{TM} Model 5984/5885

** Medtronic, Inc. Custom Model 9701-3231 Programmer

A FIFTEEN YEAR COMPARATIVE STUDY OF CARDIAC PACING COSTS

Abe Lopman, BA; Clifford L. Langer, MBA; Seymour Furman, MD, FACC; Doris J.W. Escher, MD, FACC, Montefiore Hospital and Medical Center, Bronx, N.Y.

The total cost of treating the pacemaker (PM) patient (PT) has decreased by 46% from 1965-1980. Figures are based upon: costs in dollars per PT day, costs of PM, PM longevity, PT longevity, follow-up care (i.e. clinic visits, trans telephone monitoring (TTM) calls), and personnel costs in constant 1980 dollars (U.S. Bureau of Labor Statistics). At Montefiore Hospital and Medical Center, 50% cumulative survival is 8 years after initial implant. The following table describes changing costs for treating the PM PT for 8 years of care from the point of initial implant in 1965, 1970, 1975, and 1980.

	1980*	1975*	1970*	1965*
#PM/8 Yrs	1	2	3	4
PM Life-Each (mos)	96	43,96	37,37,43	18,18,37,37
Tot PM Cost ($)	2,729	4,904	5,391	6,276
Tot Days of Hosp	6.5	15	20	29
Tot Hosp $	2,600	6,070	6,468	6,089
Tot Prof Fees ($)	1,710	2,067	2,137	1,742
Tot Staff ($)	249	406	467	573
Tot Follow-up ($)	3,971+	6,348+	6,763	6,045
8 Yr Cost/PT	11,259+	19,795+	21,226	20,725
Cost/Yr/PT	1,407+	2,474+	2,653	2,590

* Year of implant; + Projected Cost

These data reflect the reduction in costs of contemporary cardiac pacing caused by the prolongation of the PM life span, transition from outpatient visits to the less expensive TTM follow-up and present TTM schedules, and to the reduction in hospital PT days, all producing a shift from a labor-intensive service, to a modern, cost-efficient, capital-intensive mode of care.

SINUS NODE DYSFUNCTION IN SPINAL CORD INJURY WITH QUADRIPLEGIA

Thomas A. Nicosia, MD, Peter Mercurio, MD, Frederick Feit, MD, FACC, Arthur C. Fox, MD, FACC, New York University Medical Center, NY, NY.

Patients with recent spinal cord injury and quadriplegia often demonstrate sinus bradycardia (SB), sinus arrest (SA), AV block, and hypersensitivity to vagotonic maneuvers. The presumed mechanism is interruption of the sympathetic nerves to the heart, with a relative increase in parasympathetic tone.

To determine the need for permanent pacing, we examined seven patients with recent spinal cord injury and quadriplegia prospectively, 1 to 2 weeks after injury. All patients had transient SB (35-60) and SA (2-8 sec). These episodes often occurred with nasotracheal suctioning, despite prior treatment with atropine and hyperventilation. In 5 of 7 patients, His-Bundle Electrograms and sinus node recovery times (SNRT)were determined and found to be normal (A-H=100±20 msec, H-V=44±5 msec, SNRT=110%±10% of resting cycle length). In 4 of 5 patients there was no disturbance in sinus node function with carotid sinus pressure, during nasotracheal suctioning or with hypoxemia. One patient had SA (4-6 sec) with carotid sinus pressure and during suctioning. 6 of 7 patients had later episodes of SA and SB requiring permanent pacemakers.

We conclude that there is marked temporal variability in sinus node dysfunction in patients with recent spinal cord injury and quadriplegia. A normal response to sinus node testing does not assure continued normal function. We, therefore, recommend permanent pacemaker insertion in patients with recent spinal cord injury with quadriplegia who have had significant SA or SB.

ASSESSMENT OF CLINICAL EFFICACY OF A MULTIPARAMETER PROGRAMMABLE PULSE GENERATOR

David L. Hayes, MD; James D. Maloney, MD, FACC; John Merideth, MD; David R. Holmes, Jr., MD, FACC; Bernard Gersh, MD, FACC; James C. Broadbent, MD; Michael J. Osborn, MD, FACC, Mayo Clinic, Rochester, Minnesota

Recent advances in pacemaker (PM) technology have provided noninvasively programmable pulse generators (PPG) which have the potential for solving PM system complications and providing a mechanism whereby the pulse generator can be adjusted to the specific needs of the patient without compromising reliability and longevity. To assess this problem, 40 consecutive patients (pts) receiving multiparameter PPG were analyzed as to initial indications, clinical application and reliability. Data analysis of these 40 pts demonstrated that 80% (32/40) had rate changes programmed, 25% (10/40) had pulse width changes and 10% (4/40) had sensitivity programming changes. Voltage amplitude programmability was utilized in 1 patient. Hysteresis and refractory period programmability were not utilized.

Utilization of programmable features included a change of one feature in 62.5% (25/40), two features in 15% (6/40), and three or more in 5% (3/40). This multiparameter unit clearly eliminated the need for reoperation in 2 pts. Although 90% of the programming changes (rate %/or pulse width) could have been accomplished with simpler units, sensitivity programmability solved PM problems in the remaining 10% (4/40). The increased complexity of the unit has not sacrificed reliability. Strict preimplant criteria for use of such a unit is difficult because of potential clinical flexibility of the unit.

NON-INVASIVE CORRECTION OF PACING SYSTEM MALFUNCTIONS BY MULTIPROGRAMMABLE PACEMAKERS.

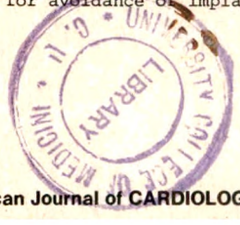
Roger A. Billhardt, MD, Stuart W. Rosenbush, MD, and Robert G. Hauser, MD, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois.

Multiprogrammable pacemakers (M) may be useful for managing post-implant pacing system malfunction (F) without need for surgical intervention. Accordingly, we assessed the value of M for correcting F in 221 consecutive patients (pts) who received lithium M from 1/1/77 to 7/1/80. The mean implant time was 11.1±10.7 S.D. mos. All M were programmable for rate and energy output; also, 135 M had mode and 52 M had sensitivity programmable features. Of 18 pts who developed F from 1 day to 24.6 (mean: 3.9± 6.7) mos after implant, 61% (11/18) were corrected by programming (Pr) without reoperation (R). Six pts had failure to capture: 4 were corrected by Pr to higher output and 2 required R. Three pts had extracardiac muscle stimulation: 1 was resolved by Pr to lower output and 2 underwent R. One pt with failure to sense was successfully managed by Pr to higher sensitivity. Symptomatic myopotential inhibition affecting 3 pts was abolished by Pr to synchronous (1/3) and asynchronous mode (2/3). One pt with after potential oversensing was corrected by Pr to lower output. Of 4 pts with intermittent failure to sense and pace, 1 was corrected by Pr to higher output and sensitivity and 3 required R. All F eliminated by Pr continue to function normally from 0.7 to 27 (mean: 7.7±7.4) mos. The mean acute/chronic thresholds and R-wave amplitudes for pts who subsequently developed F were 1.3±0.8v and 7.8±2.2mv compared to 1.2±0.6v and 8.1±1.9mv for pts who did not develop F after implant (p>.1). The 7 pts with F not corrected by Pr required lead repositioning or replacement. During the study period $56,121 in hospital costs and fees were saved by successfully managing the 11 pts with F by programming. We conclude that M are potentially valuable for correcting F noninvasively. Thus, for a substantial number of patients who receive M, the discomfort and cost of surgical intervention will be avoided.

OPERATIVE REVISION REDUCTION WITH OUTPUT PROGRAMMABLE PULSE GENERATORS

Seymour Furman, MD, FACC; Frank Pannizzo, MS, Montefiore Hospital and Medical Center, Bronx, NY

To determine whether output programmable units (OPPG) have been of clinical value we investigated post implant threshold evolution. Four groups of threshold increases existed: 1) Progressive beyond any pacer output; 2) Progressive and stable above 25 microJoules (μJ) but below 100 μJ; 3) Early peak above 25 μJ with return to a level above 10 μJ; 4) Early peak above 25 μJ with later return to "normal" chronic levels below 10 μJ. A significant increase in threshold was considered one which exceeded the energy output of a 5 volt, 0.5 milliseconds (ms) pulse duration pulse generator (PG) current limited to 10 milliamperes or a total output of 25 μJ. The output levels of each PG for initial (first implant or new lead placement) implant was calculated. For the OPPG whenever threshold exceeded 25 μJ it was assumed that cardiac stimulation would have stopped if output had not been increased. For the fixed output units, cessation of pacing was determined electrocardiographically. In 312 initial implants 30 revisions or 9.6% were performed for failure to stimulate without obvious lead displacement, facture, etc. Of 289 initial programmables, 13 required revision, or 4.5% patients with OPPG required increase in output to avoid intervention. This is a significant difference ($p = 0.15$). Output programmability provides a significant advantage for avoidance of implant revision.



MONDAY, MARCH 16, 1981
AM
CLINICAL EVALUATION OF LEFT VENTRICULAR FUNCTION
10:30-12:00

AN AUTOMATED METHOD FOR LEFT VENTRICULAR VOLUME MEASUREMENT FROM THE CINEVENTRICULOGRAPHY WITH MINIMAL DOSES OF CONTRAST MEDIUM

Masatoshi Fujita, MD; Shigetake Sasayama, MD; Hiroshi Nonogi, MD; Chuichi Kawai, MD, FACC; Shigeru Eiho, PhD; Michiyoshi Kuwahara, PhD, Otowa Hospital, Kyoto, Japan

Cineventriculography is of considerable value for the dimensional analysis of the left ventricular cavity(LVC), however, conventional methods necessiate the injection of large amounts of contrast medium(CM). To minimize the untoward effects of CM, we obtained left ventriculogram(LVG) using only 5 ml of the dye. We also developed a computer aided image processing system to enhance the contrast of the ventricular image by subtracting the reference image to eliminate irrelevant background material. The boundary of LVC was automatically determined to calculate the instantaneous volume change throughout the cardiac cycle. Using this small doses of dye, the elevation of the left ventricular end-diastolic pressure(LVEDP) which consistently occurred at 1 to 3 minutes after injection of the conventional large doses could be avoided (LVEDP at 1 minute after dye injection being averaged 11.8±4.9 vs 19.1± 6.1 mm Hg). Values for end-diastolic volume, end-systolic volume and ejection fraction calculated from the two consecutive LVG in 17 patients were similar (99±21(SD) vs 99± 22ml, 32±20 vs 34±23ml, and 66±12 vs 66±13% respectively). Thus, the small dose of CM provides for an accurate measurement of the left ventricular dimension and function without significant hemodynamic derrangement, and minimizes the additional risk to the patient undergoing examination under varying physiologic conditions. The advantage of easy repeatability of this method can be further applied to determine the optimal projections for assessing regional abnormalities of wall motion in ischemic patients with multiple exposures at various degrees of obliquity.

A NEW TECHNIQUE FOR THE SIMULTANEOUS ASSESSMENT OF MYOCARDIAL PERFUSION AND CONTRACTILITY IN MAN

Oberdan Parodi, MD; Walter Bencivelli, Dr; Paolo Camici, MD; Paolo Marzullo, MD; Graham J. Davies, MD; Attilio Maseri, MD, FACC; Antonio L'Abbate, MD, FACC.
CNR Institute of Clinical Physiology, Univ. of Pisa, Pisa, Italy

Radiolabelled human albumin microspheres (HAM) were used in the past to visualize coronary flow distribution in man. We applied gated reconstruction to HAM images to obtain information both on myocardial perfusion (MBF) and on contractility (Cy). HAM (2.5 millions sizeing 18±10 u Ø) labelled with 13 mCi of 99mTc, are injected into the LV during cardiac catheterization. Contrary to intracoronary injection, LV injection ensures homogeneous mixing of tracer and HAM distribution proportional to regional MBF. Data are collected in list mode and reconstructed off-line: this allows optimization of reconstruction parameters and the study of short duration events. By this technique, we studied as a preliminary, 15 patients with variable degree of coronary heart disease. The pattern of Cy of myocardial walls was in agreement with that observed by contrast ventriculography and by echo. The Cy of scar unperfused walls was missed: however, in these cases the main interest lies in the residual Cy of perfused walls. Advantages of the technique are: a) simultaneous information on MBF and Cy: b) prolonged time for Cy observation (4 to 6 hours); c) high quality pictures due to the favourable signal to background ratio; d) potential information on wall thickness. HAM scintigraphy gives: 1) relative to 201-Tl, a steady, true MBF pattern not affected by reperfusion or metabolism and a better imaging definition; 2) relative to gated blood pool imaging, higer quality pictures of Cy and simultaneous evaluation of MBF.

EFFECTS OF VERAPAMIL AND NIFEDIPINE ON LEFT VENTRICULAR FUNCTION IN PATIENTS WITH PRINZMETAL'S VARIANT ANGINA.

SM Johnson MD, DR Mauritson MD, J. Corbett MD, GJ Dehmer MD, JT Willerson MD, FACC, LD Hillis MD, FACC. U. of Texas Health Science Center at Dallas, Dallas, Texas.

We assessed the effects of verapamil (V) and nifedipine(N) on LV function at rest and during exercise in patients(pts) with variant angina pectoris (VAP). Each of 10 pts (6 men 4 women, mean age 52 yrs) was treated for 2 month periods with placebo(P1), V(400±80mg/day, mean±SD), and N (82±31 mg/day); 8 were maintained throughout the study on stable doses of isosorbide dinitrate(138±56 mg/day). Prior to study, all were catheterized: 8 had no fixed coronary artery disease (CAD), 1 had single vessel CAD, and 1 had 3 vessel CAD. One pt had 3 prior myocardial infarctions presumably due to coronary artery spasm. No pt had congestive heart failure clinically. The resting LV ejection fraction (EF) during P1 ranged from 26 to 84%. In each pt, equilibrium gated blood pool scintigraphy was performed at rest and during supine bicycle exercise during the final week of each of the three 2-month treatment periods. The following were measured at rest and with Ex: (1)peak achieved work load (PAWL), (2)heart rate (HR), (3)systolic blood pressure(SBP), (4)end-diastolic volume index, (5)end systolic volume index(ESVI), and LV EF.

	PAWL(kpm)	HR at PCL	ESVI at PCL	Rest EF	EF at PCL
P1	360±128	127± 9	26±25	61±18	70±19
V	357± 98	118±11	32±30	63±17	68±16
N	355±135	127±10	33±49	67±17	75±19

At rest and during the peak work load common to all 3 Ex tests(PCL), neither V nor N affected any of the measured variables. Thus, in patients with variant angina and a wide range of LV function at rest, neither verapamil nor nifedipine significantly alters exercise performance, nor do these agents adversely affect LV volumes or LV EF at rest and during exercise.

PRESERVATION OF INTERVENTRICULAR SEPTAL FUNCTION IN PATIENTS HAVING CORONARY ARTERY BYPASS GRAFTS WITHOUT CARDIOPULMONARY BYPASS

Cary W. Akins, M.D.; Charles A. Boucher, MD, FACC; Gerald M. Pohost, MD, FACC; Massachusetts General Hospital, Boston, Mass.

Abnormal interventricular septal motion develops in the majority of patients after cardiac surgery. It has been attributed by others to leaving the pericardium open or to septal ischemia. This study assesses the role of cardiopulmonary bypass in the genesis of abnormal septal motion. Eighteen patients having single coronary artery bypass grafts (CABG) to the left anterior descending or right coronary artery had septal motion evaluated pre- and postoperatively. Nine patients who had CABG with CPB were compared to 9 patients who had CABG without CPB. Patients who had normal or mildly hypokinetic septal motion before surgery, as assessed by resting gated blood pool scan or ventricular angiography, were scanned again prior to hospital discharge. Septal motion was graded as normal, hypokinetic, akinetic or dyskinetic by three independent observors.

Postoperatively all 9 patients having CABG with CPB had diminution of septal function with frank septal akinesis or dyskinesis in 7 (78%). Eight of 9 patients having CABG without CPB had no change or improvement in septal motion with only one patient developing mild hypokinesis ($p < .001$). No patient had a perioperative myocardial infarction, and in all the patients the pericardium was left open.

This study suggests that the development of abnormal septal motion in patients having single CABG is related to differential septal ischemia due to the use of CPB and/or the techniques of myocardial preservation but not to the CABG procedure itself or to leaving the pericardium open.

THE SYMPATHETIC RESPONSE TO EXERCISE IN PATIENTS WITH CONGESTIVE HEART FAILURE

Gary S. Francis, MD, FACC; Steven R. Goldsmith, MD; Jay N. Cohn, MD, FACC, University of Minnesota and the V.A. Medical Center, Minneapolis, Minn.

To assess the sympathetic response to exercise in congestive heart failure (CHF) we measured plasma norepinephrine (NE) and epinephrine (E) at rest and during maximal (max) upright bicycle exercise in 14 patients (pts). The results were compared to 6 normal subjects. Pts were in a steady state off diuretics and vasodilators. NE and E were measured using a radioenzymatic technique. Samples were taken with pts upright just prior to exercise (ex) and during peak ex. Ex capacity was determined by measuring max oxygen consumption ($\dot{V}O_2$ max). Pts were class II-IV and all had evidence of poor left ventricular (LV) function by radionuclide ejection fraction (22 ± 2.4%, SEM) and by echo (% shortening minor axis 15 ± 1.8%). $\dot{V}O_2$ max averaged 10.06 ± 1.4 ml/kg/min. The control upright NE was 636 ± 93 pg/ml and increased 171% to 1721 ± 198 pg/ml with peak ex. Plasma E increased 83% from 92 ± 18 pg/ml to 167 ± 26 pg/ml. The six normal control subjects increased NE 913% with ex (318 ± 36 pg/ml to 3220 ± 418 pg/ml), which is markedly different than pts with CHF ($p<.001$). Controls increased E 707% with ex (92 ± 26 pg/ml to 742 ± 210 pg/ml), which is also different than pts with CHF ($p<.01$). The increase in NE (% ΔNE) during ex correlated well with $\dot{V}O_2$ max ($r=.78$, $p<.001$) in pts with CHF, but % ΔE did not ($r=.23$). Catecholamines do not therefore increase to the same extent with max ex in pts with CHF as they do in normals, despite higher basal levels in heart failure pts. The ability of pts with heart failure to release NE with ex parallels their functional capacity as measured by $\dot{V}O_2$ max.

IS ISOVOLUMIC RELAXATION IMPAIRED IN SECONDARY HYPERTROPHY?

Peter Eichhorn,MS; Herta Zuend; Rosmarie Koch; Otto Hess, MD; Hans P.Krayenbuehl,MD, Medical Policlinic of the University, Zurich, Switzerland.

The speed of LV isovolumic relaxation was estimated in 56 patients (pts) with aortic valve disease (AVD) (21 AS, 18 AS+AI, 17 AI) and in 5 control subjects (group C). Pts with coronary artery disease were excluded. In all pts LV micromanometry simultaneous with single beam echos was carried out.Peak neg.dP/dt and peak neg.dS/dt (S = meridional wall stress) were used as indices of LV relaxation. Angiographic LV muscle mass was increased ($P<0.001$) in AS (179 g/m^2), AS+AI (220) and in AI (213) as compared to C (76).Peak neg.dP/dt amounted to 1491 mmHg/sec in C and did not differ from the values in the three groups of AVD although LV peak systolic pressure was higher in AS (209 mm Hg, $P<0.001$), AS+AI (190,$P<0.001$) and AI (144,$P<0.01$) than in C (114). In contrast peak neg.dS/dt was increased in AS ($1403 \cdot 10^3$ dynes/sec/cm^2, $P<0.05$), AS+AI (1467, $P<0.005$) and AI (1355, $P<0.02$) as compared to C (788). LV peak systolic S was however increased in AVD ($257 \cdot 10^3$ dynes/cm^2 in AS, $P<0.01$; 257 in AS+AI, $P<0.01$; and 212 in AI, $P<0.025$) when compared to C (128). Linear regression analysis between peak neg.dS/dt and peak S yielded significant correlations in C ($r=0.98$), in 26 pts with AVD and normal LV systolic function ($r=0.79$) and 30 pts with depressed (biplane ejection fraction <0.56, Vpm <1.14 ML/sec) LV function ($r=0.80$). Slopes and intercepts of these three regressions were similar. It is concluded that (1) in contrast to peak neg.dP/dt peak neg.dS/dt does not indicate impaired relaxation in secondary hypertrophy from AVD and (2) peak neg.dS/dt is determined by peak S regardless of the actual level of systolic LV function.

MONDAY, MARCH 16, 1981
AM
PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY
10:30–12:00

CLINICAL EXPERIENCE WITH A NEW CATHETER SYSTEM FOR PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

John B. Simpson,M.D; Ned Robert, M.D.; Donald Baim,M.D.; Donald C. Harrison, M.D.,Stanford University Medical Center, Stanford, CA. 94305

A new catheter system designed with a movable guide wire, and permitting rapid manual balloon inflation and deflation, has been used to perform percutaneous transluminal coronary angioplasty (PTCA) in 35 patients over the past 18 months. During this period, further design improvements have reduced the diameter of the 3 mm low-profile balloon catheter from 0.049" to 0.036" (tip), from 0.058" to 0.042" (collapsed balloon), and from 0.069" to 0.059" (shaft). This low-profile configuration is well suited for PTCA of high-grade stenoses of the left anterior descending, in which successful PTCA was performed in 14 of 15 patients (93%), with a reduction of the mean pre-PTCA stenosis from 89 ± 12% (range 70-99%) to a mean post-PTCA stenosis of 41 ± 24% (range 10-55%)*. No emergency coronary bypass operations were required, and there was no evidence of myocardial infarction. Restenosis at the site of successful PTCA developed in two patients (14%) -- both were successfully redilated. The mean followup period is 5.2 months (range 1-9 months). The success rate of 93% with the low-profile catheter represents a substantial improvement over the success rate of 54% with the standard profile catheter in similar lesions.

We conclude that the use of this catheter system allows safe and effective dilatation of even high-grade stenoses of the left anterior descending coronary artery, with relief of the clinical symptoms of myocardial ischemia.

* $p < 0.001$, student's paired t-test

ACUTE AND CHRONIC EFFECTS OF TRANSLUMINAL ANGIOPLASTY IN EXPERIMENTAL ATHEROSCLEROSIS

Vance J. Weber, MD; David P. Faxon, MD, FACC; Christian Haudenschild, MD; Susan B. Gottsman, AS; Wanda A. McGovern, BA; Thomas J. Ryan, MD, FACC, Boston University School of Medicine, Boston, MA

Transluminal angioplasty (TA) has received considerable attention in the treatment of obstructing atherosclerotic lesions in man; however, its mechanisms of action and effects remain unclear. To evaluate the acute and long-term consequences of TA, 30 rabbits were examined using 3 experimental models of atherosclerosis: high cholesterol diet (HCD) plus balloon de-endotheliaization (n=18); HCD plus an indwelling catheter (IC) (n=7); normal diet plus IC (n=5). Angiographic increase in luminal diameter was accomplished in 21 of 30 rabbits. In vessels showing > 50% change in luminal diameter by angiogram, (n=14), pathological examination one day after TA revealed: 1) for concentric lesions: total rupture of the intima, medial compression with disruption of the internal elastic lamina, marked inflammation and frequent thrombosis; 2) for eccentric lesions: thinning and necrosis predominantly of the normal portion of the vessel wall. Angiographic changes in luminal diameter of less than 50% were not associated with consistent histopathologic findings. In 11 rabbits examined 2 or 4 weeks after TA, further remodeling of the intima was suggested by the presence of additional loose fibrous tissue, and thrombi in various stages of organization and recanalization.

In summary, in these experimental models of TA: 1) dramatic intimal rupture, medial damage and inflammation often result; 2) proliferating intimal processes leading to luminal narrowing continue after TA; 3) marked destruction to the normal vessel wall may occur; and 4) angiographic appearance usually correlates with histopathologic findings of TA effects.

BENEFICIAL RESULTS FROM TRANSLUMINAL CORONARY ANGIOPLASTY ASSESSED BY QUANTITATIVE CROSS-SECTIONAL CORONARY ARTERIOGRAPHY

Robert K. Mito, M.D., Albert E. Raizner, M.D., FACC, John M. Lewis, M.D., FACC, William L. Winters, Jr., M.D., FACC, Richard R. Miller, M.D., FACC, Baylor College of Medicine and The Methodist Hospital, Houston, Texas.

Transluminal coronary angioplasty is a relatively new procedure, the efficacy of which is not firmly established. Quantitative assessment of stenosis severity and effects of dilatation is needed to more accurately measure its effects. Consequently, a technique of quantitating cross-sectional stenosis and normal lumen area using biplane measurements and computing area based on an elliptical model $[(a/2)^2 \times (b/2)^2 \times \pi]$ (a = short axis and b = long axis) was applied to eight patients (four native coronaries and four bypass grafts) who underwent "successful" coronary angioplasty. Before angioplasty, mean cross-sectional stenosis area was 1.36 mm^2 (range 0.45 to 2.57 mm^2) and cross-sectional percent stenosis was 84.5% (range 63.7 to 95.1%). Trans-stenosis gradient was present in seven of eight and ranged from 5 to 65 mmHg (mean 27.1 mmHg). Following angioplasty, mean cross-sectional stenosis area was 5.28 mm^2 (range 2.08 to 17.12 mm^2) ($p < .05$ from preop) and cross-sectional percent stenosis was 47.5% (range 1.3 to 85%) ($p < .01$). Mean percent improvement in stenosis was 37.0% (range 9.1 to 90.1%). Concomitantly, trans-stenosis gradient was eliminated in six of the seven patients with pre-angioplasty gradients.

Thus, improvement in stenosis severity can be documented by quantitative cross-sectional coronary arteriography and reflects hemodynamic improvement. This arteriographic technique may be applied in the serial evaluation of coronary angioplasty patients.

LEFT VENTRICULAR FUNCTION BEFORE AND AFTER SUCCESSFUL CATHETER DILATATION OF CRITICAL CORONARY STENOSES

Ulrich SIGWART MD, FACC, Milan GRBIC MD, Axel ESSINGER MD, Angelika BISCHOF-DELALOYE MD, Hossein SADEGHI MD, Jean-Louis RIVIER MD, FACC. - Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Left ventricular (LV) function was studied in seven patients one day before and six months after successful catheter dilatation(D) of critical LAD stenoses. LV and AO pressures with tipmanometers and thermodilution cardiac output were taken at rest (R) and during submaximal bicycle exercise (E) in the supine position as well as during isoproterenol (I) infusion. Ejection fraction at R and during E was estimated by gated blood pooling scintigraphy.

Hemodynamics at R before and 6 months after dilatation were not significantly different. LV EDP during E was 35.8±4.5mmHg before and 20.1±2.8mmHg 6 months after D. LV SVI at E augmented from 79±11 to 110±15ml. per beat after D. LV dP/dt max. failed to change significantly but dP/dt min. normalized from -1550±95 to -2000±110mmHg /sec. during E suggesting improved relaxation. DPTI/SPTI ratio was 0.5±0.15 before and 0.8±0.1 after dilatation, and during I abnormal LV contractility parameters improved as well. LV ejection fraction at R was normal and not significantly different before and after D ; exercise ejection fraction, however, improved after dilatation from 52±7.8% to 63±6.4%.

It is concluded that E tolerance and parameters of left ventricular function during dynamic E can be improved in patients after successful D of critical LAD stenoses.

EVALUATION OF TRANSLUMINAL CORONARY ANGIOPLASTY IN LEFT MAIN CORONARY ARTERY STENOSIS

Simon H. Stertzer, MD, FACC; Eugene Wallsh, MD, FACC; Michael S. Bruno, MD., Lenox Hill Hospital, New York, NY

Eight attempts at transluminal coronary angioplasty (PTCA) were made in left main coronary artery stenosis (LMCAS) over a 27 month period. There were 7 males and 1 female; mean age 51 years (range 45-54). All patients had multivessel coronary artery disease. Three patients had previously undergone open heart surgery (2, coronary bypass surgery (CABG); 1, aortic valve replacement). Six patients underwent PTCA via the brachial approach while 2 were treated by the femoral. All patients had Canadian Heart Class (CHA) III or IV anginal syndromes. One patient had severe preinfarctional angina requiring intraaortic balloon support. All 8 left main orifices were entered with the guiding catheter. All 8 lesions were passed with the dilatation catheter. All left main stem lesions improved initially angiographically. Mean percent stenosis before angioplasty was 75% (range 60 to 90). Mean increase in coronary distal pressure after PTCA was 48 mm Hg (range 33 to 65 mm Hg). Mean percent stenosis after left main PTCA was 32% (range 5 to 60%). All patients improved at least 1 CHA class after PTCA, and 4 were Class I. No patient died or required emergency operation. Two patients (25%) experienced recurrence within 12 months. Three patients in all required delayed CABG surgery either because of residual left main stem stenosis, recurrence, or because of remote multivessel disease. Two patients improved markedly with PTCA after CABG alone did not satisfactorily relieve their angina. The preinfarctional patient with IABP avoided surgery completely. It is concluded that despite concern regarding PTCA in LMCAS the procedure is feasible without increased risk in selected cases.

NATIONAL HEART, LUNG AND BLOOD INSTITUTE REGISTRY REPORT OF COMPLICATIONS OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Gerald Dorros, MD, FACC; Michael Cowley, MD, FACC; John Simpson, MD; Members of Executive Committee of NHLBI-PTCA Registry, Lutheran Hospital of Milwaukee, Inc., and Medical College of Wisconsin, Milwaukee, Wisconsin.

Since September, 1977, data have been collected on 632 patients (pts) who have undergone percutaneous transluminal coronary angioplasty (PTCA) from 34 centers. There were 664 PTCA's attempted with 393 (59.2%) primary successes. In 123 (19.5%) pts, there were 152 (22.9%) complications, 57 (8.6%) with sequelae and 95 (14.3%) without sequelae. The 57 complications with sequelae occurred in 52 pts (8.2%) and included: hospital deaths in 6 (0.9%) (1 directly related, 4 probably related, and 1 unrelated to PTCA); myocardial infarctions (MI) in 23 (3.5%): 11 MI's in pts with, and 12 MI's in pts without coronary artery bypass surgery (CABG) within 24 hours; coronary occlusion in 18 (2.7%); vascular complications requiring surgery in 8 (1.2%); and others, 3 (0.5%). The 95 complications without sequelae occurred in 71 (11.2%) pts and included: coronary artery dissection in 22 (3.3%); prolonged angina in 18 (2.7%); bradycardia requiring therapy in 12 (1.8%); coronary spasm in 12 (1.8%); hypotension requiring therapy in 9 (1.3%); ventricular fibrillation in 7 (1.1%); excessive blood loss in 7 (1.1%); ventricular tachycardia in 3 (0.5%); and others, 5 (7.5%). CABG was performed on 108 pts within 24 hours. There were 44 (7.0%) emergency pts, with evidence of a MI developing in 10 (22.7%). There were 64 (10.1%) elective pts. The incidence of complications occurring with PTCA, to date, is not negligible, even though the complications with sequelae are less than 10%. The mortality and morbidity with PTCA appears comparable to those reported with CABG.

MONDAY, MARCH 16, 1981
AM
VENTRICULAR TACHYCARDIA/FIBRILLATION: PREDICTION/ TREATMENT
10:30-12:00

PROGNOSTIC VALUE OF VENTRICULAR ARRHYTHMIAS
Robert M. Califf, M.D., Galen S. Wagner, M.D., Robert A. Rosati, M.D., Duke University, Durham, North Carolina

This study was designed to determine whether ventricular arrhythmias(VA) predict decreased survival independently of their association with extensive coronary artery disease(CAD) and poor LV function. Ambulatory monitoring was done for 24 hours in 611 medically treated patients after catheterization for suspected CAD. VA were grouped by modified Lown grade: 0-no VA; 1-peak hourly premature ventricular contractions(PVC's)<30: 2-peak hourly PVC's ≥30; 3-multiform PVC's; 4-2 consecutive PVC's; 5- ventricular tachycardia. Patients with higher grades had lower ejection fractions($p<.01$) and decreased survival($p<.01$).

Grade	PTS	Mean Ejection Fraction	Survival lyr.	Survival 3yrs.
0-1	363	57	98%	95%
2-3	179	51	93%	86%
4-5	69	41	82%	69%

A score based on VA grade was the most potent predictor of cardiovascular death among descriptors of VA($X^2=32$). When considered with a group of 20 catheterization measurements in multivariable analysis, VA had no independent prognostic significance. LV end diastolic pressure and number of vessels with ≥75% stenosis were the most powerful predictors in multivariable analysis.

In the 361 patients with normal LV contraction, VA grade was not related to survival.

Grade	PTS	Survival lyr.	Survival 3yrs.
0-1	260	99%	98%
2-3	84	98%	98%
4-5	17	100%	92%

In these patients with symptoms of CAD, VA were associated with decreased survival because they reflected advanced CAD and LV dysfunction. A group with normal LV function at risk due to VA could not be identified.

PREDICTIVE VALUE OF PROGRAMMED ELECTRICAL STIMULATION IN PATIENTS WITH SUDDEN DEATH OR RECURRENT VENTRICULAR TACHYCARDIA. Edward V. Platia, MD, Stephen C. Vlay, MD, Philip R. Reid, MD, FACC. Johns Hopkins University, Baltimore, Maryland.

Programmed electrical stimulation (PES) was carried out in 48 patients (pts) referred for evaluation of sudden cardiac death(SD) (17 pts) and/or recurrent ventricular tachycardia (VT) (30 pts) and in 11 controls. PES included: 1)single ventricular premature depolarization(PVD) after atrial drive(A_1V_1);2) single PVD following V drive (V_1V_2); 3) double PVDs following V drive ($V_1V_2V_3$); and 4) rapid V pacing for 10 consecutive beats (V_{burst}). At least 3 quadripolar catheters were used:right atrial, right and/or left ventricular and His catheters. A positive response was defined as 2 or more ventricular premature beats produced by the final ventricular pacing stimulus occurring by intraventricular reentry. Forty SD/VT pts underwent PES with the $V_1V_2V_3$ technique and 17 of 28 with a positive test by this technique,including 6 pts with sustained VT, had SD or recurrent VT following hospital discharge, while only 1 of 12 with a negative test had SD or recurrent VT in follow-up(range 1-13 months)($p\leq.007$). None of the 11 control pts had a positive response with any technique. The positive predictive value (PPV) was therefore 61%, while the negative predictive value was 92%. Twenty-eight of the 40 pts were found to be on the same drug regimen in follow-up as during PES. Of this group, subsequent SD or recurrent VT occurred significantly more frequently (PPV=71%) if electrophysiologic testing with $V_1V_2V_3$ technique yielded a positive result (15 of 21) compared to a negative result (1 of 7)($p\leq.03$). The other 3 techniques, A_1V_1, V_1V_2, and V_{burst} were not significantly predictive of subsequent SD or VT, the PPVs being 22%,47% and 50% respectively. In conclusion, in pts with a history of sudden death or recurrent ventricular tachycardia, PES carried out with the $V_1V_2V_3$ pacing technique is predictive of the occurrence of subsequent sudden death or ventricular tachycardia and appears to be superior to the A_1V_1, V_1V_2 and V_{burst} techniques.

PREVALENCE AND SIGNIFICANCE OF VENTRICULAR TACHYCARDIA IN THE LATE HOSPITAL PHASE OF MYOCARDIAL INFARCTION
J. Thomas Bigger, Jr., MD, FACC; Francis M. Weld, MD, FACC: Linda M. Rolnitzky, MS, Columbia University, New York, N.Y.

There are no large studies which determine the significance of ventricular tachycardia (VT) two weeks after myocardial infarction (MI). Accordingly, we evaluated the prevalence and significance of VT in 430 MI patients studied just before discharge from hospital. A 24-hour Holter ECG was recorded and analyzed by digital computer. Fifty patients (11.6%) had VT. The VT group had significantly more :previous MI; LV failure, atrial fibrillation and VT/VFIB in the CCU; and more posthospital treatment with digitalis, diuretics and antiarrhythmic drugs. There was no significant association between age, site of MI or peak creatine kinase and the occurrence of VT. Only a single episode of VT occurred in 25 patients (50%); the average number of episodes was 21±72. The longest run of VT was only three complexes in 16 patients (32%). The average number of QRSs in VT was 11±35. The average rate of VT was 123±33 beats/min and R on T started VT in only three patients (6%). The correlation between VT and heart rate was not significant ($r=0.14$). There was no relationship between time of day and occurrence of VT. In the first year after MI, 64 deaths occurred (15%). Mortality in the VT group was 40% compared to 12% in the non-VT group. VT had the strongest association with one year mortality of any variable examined. Also, the association of VT with death was independent of many other risk factors. We conclude that asymptomatic, self-limited VT is a specific, potent and independent risk factor for death in the year after MI.

ELECTROPHYSIOLOGIC STUDIES BEFORE AND AFTER IMPLANTATION OF THE AUTOMATIC DEFIBRILLATOR. Philip R. Reid, MD, FACC; M. Mirowski, MD, FACC; Morton M. Mower, MD, FACC; Stephen C. Vlay, MD, Edward V. Platia; Myron L. Weisfeldt, MD, FACC. Johns Hopkins Hospital and Sinai Hospital, Baltimore, Maryland.

Programmed electrical stimulation (PES) studies were performed in a group of 6 patients (pts)(age 16-72 years) who underwent implantation of the automatic defibrillator (AD) in order to determine their suitability as candidates for implantation and to evaluate AD performance post-operatively. All pts were survivors of multiple episodes of sudden cardiac death and were refractory to conventional and investigational drug therapy. The 4 PES studies which were done prior to AD implant demonstrated easily inducible sustained or nonsustained ventricular tachycardia or flutter (VT/VF). After AD implant PES was performed in 5 pts (one pt developed spontaneous VT post-op which obviated need for PES), using either standard PES techniques or a train of impulses (60-100Hz)if needed, resulting in hypotensive VT/VF (333 to 222ms) which were similar to the native dysrhythmias. The AD identified the arrhythmias in all cases and discharged after an average of 30.8sec (range 18-50 sec.),restoring a normal rhythm in 3 cases. In two pts, the induced VT/VF was not corrected on the initial automatic countershock and external cardioversion was successfully used. One of these two pts subsequently died with presumed out-of-hospital sudden death which may indicate the need for higher defibrillation energy requirement. In the second pt, review of electrograms raised question of low-level 60Hz interference which could alter AD function. In 2 pts, 7 episodes of VT occurred spontaneously, all of which were correctly identified and converted by the AD. These preliminary studies demonstrate that the AD is capable of correctly identifying and converting potentially lethal VT/VF and that PES in these high risk pts may offer a safe and useful adjunct to AD evaluation.

Low Energy Versus High Energy Defibrillation in the Treatment of Out-of-Hospital Ventricular Fibrillation. A Preliminary Report.
W.Douglas Weaver,MD,FACC;Leonard A.Cobb,MD,FACC;Michael K. Copass,MD;Alfred P.Hallstrom,PhD,University of Washington, Seattle, WA.

The efficacy of defibrillation using 175J was prospectively compared to 320J in 95 victims of ventricular fibrillation (VF) treated outside the hospital. By random allocation, 46 patients (pts) received 175J and 49 received 320J for the first two shocks; all subsequent shocks were 320J in both groups. Ten of the 175J group (22%) and 8 of the 320J group (16%) persisted in VF through two shocks. Twenty-nine pts in each group were resuscitated and transported to the hospital. Fourteen of 38 pts (37%) in the 175J group and 12 of 41 (29%) in the 320J group survived and returned home (8 in each group are still hospitalized). The 175J group received an average of 4.7 shocks compared to 3.4 in the 320J group ($p < 0.05$); but this difference occurred only in non-resuscitated pts (6.6 vs 4.0 shocks in the 175J vs the 320J group respectively, $p < 0.025$). Pts discharged alive (both groups) received fewer shocks than did those who were resuscitated and later died in the hospital, (2.4 vs 4.6, $p < 0.005$). At the end of the two shock trial, the ECG showed the following rhythms in the 175J and 320J groups: VF 35% vs 20%; asystole 7% vs 20% ($p < 0.05$); idioventricular 15% vs 16%, and supraventricular 43% vs 43%. Following the first two shocks, 3 pts (7%) in the 175J group compared to 10 (20%) in the 320J group had demonstrated high degrees of AV block ($p < 0.05$).

We conclude that two low energy shocks appear to be safe in the treatment of out-of-hospital VF, that outcome appears at least as good as that obtained with 320J, and that there may be less cardiotoxicity as measured by resulting asystole and AV block.

TWO DIMENSIONAL ECHOCARDIOGRAPHY OF THE HEART DURING CARDIOPULMONARY RESUSCITATION IN MAN
Stuart Rich, MD; Hershel L. Wix, MD; Edward Shapiro, MD, University of Chicago, Chicago, Illinois.

Recent animal studies have challenged the notion that compression of the heart between the sternum and spine causes blood flow during closed chest CPR. We performed 2-D echocardiography (2DE) within 20 minutes after the initiation of CPR in four patients (ages 58-84 yrs., 3 with coronary artery disease, 1 with congestive cardiomyopathy) who had cardiac arrest while in the intensive care unit. Each patient had arterial pressure monitoring that confirmed the effectiveness of the CPR. None of the patients survived resuscitation. Analysis of the 2DE showed that the mitral and aortic valves were open simultaneously during the compression phase, suggesting blood flow directly from the lungs to the AO. Blood flow into the RV, as seen with saline bubble contrast, occurred during the relaxation phase. Measurements of the heart made from the parasternal long-axis view showed: 1) no appreciable reduction in LV dimension during compression (average 2.8%, range 1.9-3.8%); 2) the reduction in LA and RV outflow tract dimension with chest compression averaged 22.8% and 52.7% respectively. Our study confirms that the flow of blood from the heart generated by chest compression during CPR is not caused by compression of the LV and supports the evidence that blood flow during CPR results from changes in intrathoracic pressure. Blood flow from direct compression of the LA and AO may be a factor in some patients.

MONDAY, MARCH 16, 1981
PM
PHARMACOLOGY: CALCIUM ANTAGONISTS I
2:00-3:30

THE PLACEBO RESPONSE IN VASOTONIC ANGINA-A CRITICAL FACTOR IN DRUG TRIAL DESIGN.
Rose M. Robertson, MD, FACC; Yvonne Bernard, RN; David Robertson, MD, Vanderbilt Medical Center, Nashville TN.

Many agents have been thought efficacious in vasotonic angina(VA) because a decrease in ischemic episodes followed their administration. We analyzed more than 1500 episodes of VA in 10 patients(pts) (ages 38-72;6 female,4 male) admitted to hospital for diagnosis and therapeutic trials. All pts had chronic recurrent episodes of myocardial ischemia which were not preceded by a rise in heart rate or intra-arterial pressure. Coronary anatomy ranged from angiographically normal (1 pt) to 90% stenosed (1 pt), with 7 pts having 30-50% narrowings. We performed all trials in a random-order, double-blind, placebo(PLA)-controlled fashion, with continuous ECG recordings throughout. An initial PLA run-in period of 2-4 days was followed by multiple cross-overs back to PLA between trials of therapeutic agents. We tabulated the frequency of ischemic episodes on initial PLA days and during days of later PLA periods more than 5 half-lives removed from active agents. Two patterns emerged. Two pts had stable VA, with 12-37 episodes of ischemia/day, unchanging over 6 weeks of observation. All other pts had a gradual decrease in the frequency of episodes, often mimicking a therapeutic response. In 6 of 8, the decrease on PLA day 2 ranged fro 20-100%. By the third PLA period, 4 pts had complete remission of episodes. Seven of the 8 pts had no more than 2 episodes/day by the fourth PLA period. The mean decrease in the daily number of ischemic episodes over the total hospital stay was 91% for these 8 pts, from a mean of 15/day to a mean of 2/day, ($p < 0.05$). We conclude that complete or near-complete remissions are characteristic of vasotonic angina. An inherent decrease in the frequency of ischemic episodes may easily confound the interpretation of therapeutic trials.

A COMPARISON OF VERAPAMIL AND NIFEDIPINE IN PATIENTS WITH PRINZMETAL'S VARIANT ANGINA PECTORIS.
SM Johnson, MD, DR Mauritson, MD, JT Willerson, MD, FACC, LD Hillis, MD, FACC, U of Texas Health Science Center, Dallas, TX.

The present study was performed to assess the relative efficacies of verapamil (V), nifedipine (N), and placebo (P) in the therapy of patients (pts) with variant angina pectoris (VAP). In 10 pts (6 men, 4 women, mean age 52 yrs) with VAP, V (400 ± 80 mg/day, mean$\pm$SD),N (82 ± 31 mg/day) and P each were administered for 2 months. Eight of the 10 pts were maintained throughout the 6 months of study on a stable dose of isosorbide dinitrate (138 ± 56 mg/day). Prior to study, all had cardiac catheterization: 8/10 had no fixed coronary artery disease (CAD), 1 had 1 vessel CAD, and 1 had 3 vessel CAD. Two of the 10 had been resuscitated from sudden cardiac death prior to study. During each 2-month period, the following were quantitated: (1)chest pains/week (wk), (2)nitroglycerin used/wk, and (3)required hospitalizations (HOS) for clinical instability. With both V and N, the number of chest pains/wk and the number of NTG used/wk were less than with P. During P, 4 pts required a total of 5 HOS for clinical instability; during N, 2 pts required such, whereas no pts required HOS during V.

	chest pains/wk	NTG/wk	HOS/2 months
P	15.9 ± 37.2	18.2 ± 44.0	5
V	2.2 ± 3.2*	3.2 ± 5.3*	0*
N	1.2 ± 1.5*	2.3 ± 4.1*	2

(*$p < 0.05$ when compared to P) V caused mild constipation in 2/10 pts not requiring a change of dosage; in contrast, N induced orthostatic dizziness in 3/10, substantial headache in 2/10, and pedal edema in 1/10, all necessitating a reduction in dosage. Thus, (1)verapamil and nifedipine demonstrate similar efficacy in the treatment of variant angina, although (2)in this small number of patients, nifedipine was associated with more substantial side effects than either placebo or verapamil.

VERAPAMIL IN THE TREATMENT OF PRINZMETAL'S VARIANT ANGINA: A LONG-TERM, DOUBLE-BLIND, RANDOMIZED TRIAL. SM Johnson, MD, DR Mauritson, MD, LD Hillis, MD, FACC, JT Willerson, MD, FACC, U of Texas Health Science Center, Dallas, TX.
This study was performed to assess the efficacy of verapamil (V) in patients (pts) with variant angina pectoris (VAP). In 13 pts (8 men, 5 women, mean age 52 yrs) with VAP, V (388±76 mg/day, mean±SD) was compared to placebo (P) in a double-blind, randomized, double-crossover trial of 9 months duration: 1 month of open-label V followed by four 2-month periods of blinded therapy (V-P-V-P or P-V-P-V). Ten of 13 pts were maintained on stable doses of isosorbide dinitrate (128±55 mg/day) throughout the study. During each 2-month period, the following were quantitated: (1)chest pains/week (wk), (2)nitroglycerin (NTG) used/wk, and (3)required hospitalizations (HOS) for clinical instability. During the 4 months of V, the number of chest pains/wk (2.0±3.5) and the number of NTG/wk (2.5±4.5) were less ($p<0.01$) than during P (12.1±27.8 pains/wk, 15.7±37.5 NTG/wk). None of 13 required HOS during V, but 4/13 required a total of 5 HOS during P ($p<0.05$). Of the 13 pts, 6 had clinical activity throughout the study, but the other 7 (54%) had prolonged periods of inactivity which, in 6/7, lasted the entire 8 months. In the 6 active pts, V had a marked salutary effect (3.8±3.1 pains/wk, 4.6±5.7 NTG/wk) when compared to P (24.7±36.2 pains/wk, 30.1±49.8 NTG/wk, $p<0.01$). V was well tolerated, causing only minor constipation not requiring a change of dosage. Thus, (1)many patients with variant angina have prolonged periods of clinical quiescence even without calcium antagonists, emphasizing the need for properly-designed studies of potential therapeutic agents; and (2)in a long-term, double-blind, randomized study, verapamil is safe and efficacious in the treatment of variant angina and is especially beneficial in those with clinically-active disease.

BENEFITS OF ADDED NIFEDIPINE IN UNSTABLE ANGINA PERSISTING DESPITE BETA BLOCKADE AND ISOSORBIDE DINITRATE
Frans Hagemeijer, MD, FACC, Sint Franciscus Gasthuis and Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

Unstable angina (UA) consisting of angina at rest associated with reversible ischemia on the ECG was treated with bed rest, oxygen, sedation (diazepam 5 mg tid), beta blockade to slow heart rate to <60/min (metoprolol 50-200 mg/day) and isosorbide dinitrate (5 mg every 2 hours). Despite therapy UA persisted in 45 patients (pts), 31 men and 14 women aged from 33 to 81 (mean: 61.6); 33 pts had a prior myocardial infarction (MI), 11 of them <10 days before the onset of UA. Nifedipine (60 mg/day) was added to the previous drugs. UA remained unstable in 8 pts but was stabilized during at least 1 month in 37 pts. The Table shows the 1-19 months (mean: 10) follow-up of these pts and occurrence of MI or coronary artery bypass surgery (CABS) according to the severity of residual angina: invalidating (I), serious (S), moderate (M) or absent (A) with medication:

	Persisting UA	Severity of stabilized UA				Total
		I	S	M	A	
Age >70	1	2	3	5	2	12
MI	1	1	0	0	0	1
Age <70	7	4	5	10	6	25
MI	3	0	0	1	0	1
CABS	4	4	5	1	0	10

Nifedipine caused transient headache in 7 pts, leading to cessation of the drug in 1 pt.

Nifedipine thus proved to be a valuable addition to conventional therapy for UA, suggesting that coronary artery spasm is an important contributing factor in this syndrome.

SATURABLE METABOLISM OF PERHEXILINE MALEATE: CORRELATIONS WITH LONG-TERM TOXICITY
John D. Horowitz, MB; Pamela M. Morris, BSc; Olaf Drummer, MSc; Alan J. Goble, MD; and William J. Louis, MD, Departments of Cardiology and Clinical Pharmacology, Austin Hospital, Heidelberg, Victoria, Australia.

Perhexiline maleate (Px) is a calcium channel antagonist which is an effective prophylactic anti-anginal agent, with minimal cardiovascular adverse effects. However, the chronic administration of Px may cause hepatitis or peripheral neuropathy, limiting the clinical usefulness of Px, which is cleared largely by hepatic hydroxylation. The current investigation examines the possibility of a pharmacokinetic basis for these adverse effects. Single-dose pharmacokinetic studies were performed in six patients with severe angina pectoris using oral Px doses of 150 and 300 mg. A sensitive (threshold 5 ng/ml) and specific high performance liquid chromatographic assay was used. Doubling of the Px dose was associated with a prolongation of mean elimination half-life (from 11.2±2.1 S.E.M. to 19.1 ±2.8 hours; $p<0.01$) and a disproportionate increase (mean 5.3-fold) in area under the plasma concentration-time curve suggesting saturable hepatic hydroxylation of Px. Steady-state studies in 17 patients treated with Px indicated a therapeutic plasma concentration range of approximately 150 to 600 ng/ml. Five cases of Px toxicity (2 of peripheral neuropathy, one each of hepatitis, blurred vision and nausea) were all associated with Px levels above 700 ng/ml (mean 1570±370 ng/ml), and were reversible with readjustment of Px dosage. We conclude that Px is a long-acting calcium channel antagonist which is prone to accumulate in some patients due to limited capacity for hepatic Px metabolism. Monitoring of plasma Px concentrations at regular intervals will permit optimization of long-term therapy with Px.

ANTIPLATELET EFFECTS OF VERAPAMIL IN MAN

Sergio Chierchia, MD; Filippo Crea, MD; Walter Bernini, Gianfranco Gensini, MD; Oberdan Parodi, MD; Raffaele De Caterina, MD; Attilio Maseri, MD; FACC, Istituto di Fisiologia del C.N.R. Pisa

We studied the "in vivo" and "in vitro" effects of verapamil (V) on human platelets. Platelet rich plasma was obtained by 20 healthy volunteers and Thrombin (T), Collagen (C), ADP and Adrenaline (A) induced platelet aggregation (Born) was assessed after a 20 min incubation with 3 increasing concentrations of V ($4x10^{-6}$, $4x10^{-5}$ and $4x10^{-4}$ M). A dose dependent decrease in "in vitro" platelet aggregation was observed, more pronounced for C and A.

V	ADP	T	C	A
$4x10^{-6}$ M	-8±6*	+17±12	-29±22*	-16±11*
$4x10^{-5}$ M	-31±10**	-15±23	-58±28**	-73±9**
$4x10^{-4}$ M	-52±10**	-51±15**	-97±2***	-100±0***

*$p<0.05$; **$p<0.01$; ***$p<0.001$

In 9 coronary patients with an abnormal platelet function, V was given i.v. for 30 min at a rate of 5μgr/Kg/min under continuous ECG and pressure (AP) monitoring. Platelet circulating aggregates (PCA), platelet cAMP and thromboxane B_2 (TxB_2, RIA) were measured during control, at 3, 15, 30 min of infusion and 30, 60, 90 min after. In all subjects V produced, within 3 min, a progressive decrease in PCA (55±7% $p<0.01$), associated with a drop in systolic AP (14±3% $p<0.01$) and with an increase in HR (11±2%, $p<0.05$). All these effects persisted up to the end of V infusion. AP and HR returned to the baseline within 90 min while PCA were still reduced, although not significantly. No changes in plateled cAMP and TxB_2 were noted. We conclude that V exerts both in vitro and in vivo remarkable antiplatelet effects, probably related to its slow-channels blocking properties. This additional pharmacological effect could be advantageous in the management of coronary patients.

MONDAY, MARCH 16, 1981
PM
CORONARY ARTERY DISEASE: SURGICAL CONSIDERATIONS
2:00-3:30

THE PROGRAM ON THE SURGICAL CONTROL OF THE HYPERLIPIDEMIAS (POSCH): A STATUS REPORT

Richard B. Moore, MD, FACC; Henry Buchwald, MD, FACC; Richard L. Varco, MD; John M. Long, EdD; John P. Matts, PhD; and the POSCH Group, University of Minnesota Medical School, Minneapolis, Minnesota.

The POSCH is a multicentered NHLBI-funded CHD secondary intervention clinical trial of the lipid-atherosclerosis hypothesis using partial ileal bypass surgery(PIB) to effect maximal plasma lipid reduction in subjects (30-64 yrs, free of diabetes, hypertension, obesity) with one documented myocardial infarction. Of the first 286 male subjects 149 were normo- and 137 were hyper-lipoproteinemic (53-IIA, 16-IIB, 68-IV). At baseline there were no significant differences in plasma total cholesterol (C), triglycerides (TG), or lipoprotein (VLDL, LDL, HDL)-cholesterol concentrations between 153 Control and 133 PIB subjects. Baseline values for PIB Group (mean± SD):

TYPE	n	C	TG	VLDL	LDL	HDL
N	70	242±14	164±47	23± 7	177±14	41.0±9.7
IIA	25	298±48	159±47	22± 8	237±47	42.5±9.4
IIB	7	303±22	275±65	54±19	216±13	40.0±11.3
IV	37	258±30	365±166	61±25	158±29	35.5±6.5

At 3 yrs Controls had a 11% reduction in HDL-C (36.7 vs 41.0 mg/dl, $p<.01$) but no significant changes in the other plasma lipids; the PIB Group had significant($p<.001$) reductions of 30% in C (181 vs 250 mg/dl) and 43% in LDL-C (106 vs 186 mf/dl) and a 1.1% increase (NS) in HDL-C. There was a 3.7 mg/dl difference in HDL-C between PIB and Control at 3 yrs ($p<.05$). PIB is lasting, safe, obligatory in its action, and highly effective resulting in a marked reduction in the major atherogenic lipoprotein (LDL) and a relative increase in the "protective" lipoprotein (HDL).

CORONARY BYPASS VS MEDICINE: PROBLEMS AND GUIDELINES IN ASSESSING MORTALITY DIFFERENCES

Frank E. Harrell, Jr., Ph.D., Kerry L. Lee, Ph.D., David B. Pryor, M.D., Robert A. Rosati, M.D., Duke University Medical Center, Durham, North Carolina

Assessing the effect on survival of coronary bypass surgery(S), especially in series where the treatment is not randomly assigned, is complicated by early medical (M) deaths and treatment selection bias. Some reports exclude early M deaths from analysis, but differing definitions of "early" can alter the results. The approach used in adjusting for treatment selection also affects assessment of S.

Of 2630 consecutive patients(PTS) catheterized for chest pain at Duke University Medical Center having significant (≥75%)coronary stenosis, there were 1504 M and 1126 S PTS. One year survival for all M PTS was .913. S PTS to be counted as such had to survive from catheterization to operation. Crediting to M this additional survival time (median, 3 weeks)improves the estimate to .926. In 209 PTS with significant left main disease (87 M, 132 S, median time to operation 2 weeks), this adjustment improves one year M survival estimates from .676 to .733. Statistical methods exist to adjust for baseline factors and analyze the S effect treating every S PT as an M PT until surgery.

Compensating for treatment selection bias by adjusting for baseline prognostic factors is a major problem. Experimenters frequently adjust only for factors imbalanced between treatment groups. Depending on the meaning of "balance", this method can lead to varying conclusions. For example, suppose 7 M PTS had ejection fraction(EF) of .1,.2,.3,.4,.5,.6,.7 and 3 S PTS had EF of .3,.4,.5. Statistical tests indicate no differences in average EF. If only the M PTS with EF<.3 died, S would appear to have an effect; adjusting for EF removes the effect. One should adjust for factors even weakly related to survival in either M or S.

CURRENT RISK SURROUNDING CORONARY BYPASS SURGERY

D. Craig Miller, MD, FACC; Edward B. Stinson, MD, FACC; Philip E. Oyer, MD; Bruce A. Reitz, MD; Stuart W. Jamieson, MB, BS; Norman E. Shumway, MD, FACC; Stanford University School of Medicine, Stanford, California.

Contemporary reassessment of the changing operative risks associated with coronary artery bypass(CABG) surgery is useful to facilitate clinical decision-making and comparative analysis. Two groups of consecutive patients(PT) undergoing isolated CABG were compared: Group A(1971-75, n=1,000) and Group B(1979,n=437). The latter group was older and had more advanced disease and LV dysfunction as evidenced by the following preoperative variables(A vs B): age-54 vs 59 yr*; CHF-20% vs 26%***; NYHA IV=18% vs 33%*; unstable angina-27% vs 55%*; carotid disease-2% vs 5%**; LV dyskinesis-4% vs 7%***; LVEDP-11.6 ± 0.3(± SEM) vs 15.1 ± 0.4 torr*; ejection fraction-61 ± 1% vs 56 ± 1%**; number of vessels diseased-2.7 ± 0.04 vs 3.2 ± 0.06*. Although fewer CABG/PT(2.4 ± 0.03 vs 2.9 ± 0.04*) were performed and adjunctive endarterectomy was carried out less frequently(9% vs 16%**) in Group A, average ischemic time(55 ± 0.7 vs 52 ± 0.8 min**) and CPB time (109 ± 1 vs 93 ± 1 min*) were significantly longer. More importantly, the incidence of perioperative myocardial infarction declined from 8.7% in Group A to 2.7% in Group B($p < 0.0005$) and the operative mortality rate fell from 2.4% to 0.7%($p=0.017$). Patient selection was clearly not responsible for these improved results. These contemporary risks should be considered in the clinical decision-making process instead of results obtained during the earlier phases of the evolution of coronary surgery.

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*$p < 0.0001$; **$p < 0.01$; ***$p < 0.05$

THE POTENTIAL ROLE OF INTRAVENOUS ANGIOGRAPHY IN MANAGEMENT OF CARDIAC SURGERY PATIENTS

W.D. Turnipseed, MD; P. D. Myerowitz, MD; A.B. Crummy,MD; C. Strother, MD; J. Sackett, MD; C. Mistretta, PhD; C. Shaw, D. Ergun; University of Wisconsin Hospitals, Madison, Wisconsin

Although arteriography is essential for precise definition of surgically correctable lesions it is of limited value as a method of diagnostic screening and postop assessment in coronary artery and peripheral vascular patients. Recent developments in computerized image enhancement make it possible to visualize coronary artery grafts and peripheral vascular system by intravenous injection of iodinated contrast media, and promises to expand the traditional role of arteriography without many of the dangers of direct arterial catherization. The technique is performed by power injecting 40-60 cc of contrast media through a #16 angiocath into an arm vein. After injecting contrast media, a mask image is taken followed by either a sequence of 6-10 static images taken at 1.5 second intervals or a continuous fluoroscopic sequence. A digital video processor subtracts images from the mask producing contrast enhanced arterial images that can be converted to hard copy arteriography by multiformat camera or stored on video tape. Intravenous angiography can accurately identify plaquing, stenosis, occlusion and aneurysmal changes in arteries peripheral to the heart and distinguish occlusion from patency in coroary bypass grafts. The ability to easily obtain accurate anatomical detail of the carotid and extremity vessels may allow more precise definition of preoperative risk factors in candidates for elective coronary artery bypass and provides an excellent means for determining graft patency after coronary artery bypass surgery. Postoperative ventriculography can also be performed by this method.

EVALUATION OF AORTOCORONARY BYPASS GRAFT PATENCY STATUS BY COMPUTED TOMOGRAPHY

Frederic R. Kahl, M.D., FACC; Neil T. Wolfman, M.D.; L. Earl Watts, M.D., FACC, Bowman Gray School of Medicine, Winston-Salem, NC

The efficacy of contrast enhanced computed tomography (CT) to define graft patency status was studied in 42 patients with 100 aortocoronary bypass grafts. The status of each graft had been determined earlier by angiography. A rotary fan beam whole body scanner with a 2 second scan duration was used. Initial scans determined the optimal level for study of the graft; patency was assessed by CT enhancement of the graft after bolus intravenous injection of 30 ml meglumine and sodium diatrizoate. The CT studies were evaluated without knowledge of the angiographic findings; graft status by CT was interpreted as either patent, occluded, or equivocal.

Overall, CT correctly defined graft patency status in 79/100 grafts, incorrectly defined graft status in 9/100 grafts, and, in 12/100 grafts, the CT diagnosis was equivocal. CT correctly identified 61/74 patent grafts and 18/26 occluded grafts. Patency status was correctly defined by CT in 35/37 grafts to the left anterior descending coronary artery, in 23/30 grafts to the circumflex branches, and in 19/31 grafts to the right coronary artery.

These data indicate that CT is a promising non-invasive method of determining patency of aortocoronary bypass grafts, especially in grafts to the left anterior descending coronary artery.

CHANGES IN LATE CORONARY ARTERY BYPASS GRAFTS: THE VARIABILITY OF THEIR INTIMAL ATHEROSCLEROSIS.

Bernadine H. Bulkley, M.D., F.A.C.C., The Johns Hopkins School of Medicine and Hospital, Baltimore, Maryland.

Long-term success of coronary artery bypass surgery will, in large part, be determined by the fate of the implanted vein graft. Early intimal changes have been described, but little is yet known about grafts implanted for months to years. In this study, 48 grafts implanted in 24 autopsied patients from 1 month to 9 years (average 260 months) were evaluated by postmortem angiography, gross and histologic examination, and findings correlated with anastomosis patency and implantation period. Of the 24 patients, 83% had at least one patent graft. The lumen of 15 of the 48 grafts (31%) were narrowed by > 50% by an intimal fibrous lesion histologically identical to atherosclerosis; in one graft implanted for 9 years, a complicated atheroma had formed with necrotic debris and extracellular lipid. The development of graft atherosclerosis varied within patients, and from patient to patient, with only limited relationship to duration of implantation: 7 of 15 (47%) narrowings of grafts in excess of 50% of their lumen were in grafts implanted for over 2 years (average 4.6), but the remaining 8 focal graft narrowings developed in ones implanted from 2 to 8 months. In 9 grafts severe intimal lesions were associated with stenosis or occlusion at the coronary anastomosis site.

Thus, although period of implantation is one variable in graft atherosclerosis, other factors including the hemodynamics of the graft appear as important and needs further clinical and pathologic study.

MONDAY, MARCH 16, 1981
PM
DIVERSE ASPECTS OF CARDIOMYOPATHY
2:00-3:30

USEFULNESS OF SEPTAL ENDOMYOCARDIAL BIOPSY FOR EARLY DIAGNOSIS OF CHAGASIC CARDIOMYOPATHY.

Hugo A. Carrasco G. MD; Ernesto Palacios, MD; Cecilia Scorza, MD; Antonio Rangel, MD; George Inglessis MD; FACC; Abdel Fuenmayor, MD. Universidad de Los Andes. Mérida. VENEZUELA.-

There is no current world medical information about myocardial biopsy studies in Chagas'disease. We present the ultrastructural, histopathologic and inmunologic findings from 180 septal endomyocardial biopsies taken in 60 chagasic patients via percutaneous jugular approach. No complications were observed. All studies were interpreted following a specially designed cytogram; patients were classified into four evolutive groups: IA: no cardiac disease. IB: early myocardial damage by left cine-ventriculogram only; II: advanced myocardial damage with abnormal EKG and left cine-ventriculogram, and III: clinical congestive heart failure. Sixty percent of group IA patients had evident degenerative changes, decreased mitochondrial and miosine ATPase activity and increased mono amino-oxidase (MAO) activity indicative of myocardial damage. Ninety percent of group IB patients had similar, although more advanced changes, with added increased lysosomal activity. Almost everyone patient of groups II and III (95 and 100%) had severe ultrastructural and histochemical abnormalities with increased incidence of lipids and glycogen deposits, cellular infiltrates and fibrosis. The myocardial biopsy is the most sensitive method currently available for diagnosis of early myocardial damage in Chagas' disease, since it could detect evident abnormalities in 60% of otherwise "normal" chagasic patients. It could also be useful for following the evolution of myocardial lesions, for evaluating therapeutic effects and for studying of its patho - genetic mechanisms.

RADIONUCLIDE ANGIOGRAPHY AND ENDOMYOCARDIAL BIOPSY IN THE ASSESSMENT OF DOXORUBICIN CARDIOTOXICITY.

Maurice Druck, MD, Ben-Zion Bar-Shlomo,MD, Karen Gulenchyn,MD, David Hilton,MD, George Jablonsky,MD, Avrum Gotlieb,MD, Malcolm Silver,MD, Patricia McEwan,MD, David Feiglin,MD, John Morch,MD, Wm. Evans,MD, Peter McLaughlin,MD,FACC, Toronto General Hospital, Toronto, Ontario Canada.

We studied 33 patients (Pts) with a mean age of 53 yrs (20-75 yrs), who were receiving doxorubicin (D) for malignant disease, to determine the relationship between functional and morphological changes in the myocardium at different dose levels of D, Serial Pt evaluations included physical examination, chest x-ray, ECG, endomyocardial biopsy (EMB), and rest and exercise gated nuclear angiograms (GNA) at doses of D ranging from 1440954mg/m^2 (mean 452mg/m^2). Abnormalities of physical examination, chest x-ray and ECG were insensitive predictors of D cardiotoxicity. Correlation of GNA and EMB on 27 Pt evaluations are presented:

		GNA	
		NORMAL (N)	ABNORMAL (ABN)
EMB	NORMAL	0	0
	ABNORMAL	9	18***

N=27

*Included are 5 Pts with normal rest GNA but abnormal exercise response. **All Pts with resting EF 45% had significant abnormalities of EMB.

We conclude:

1. The good correlation between GNA and EMB in detecting early D cardiotoxicity allows GNA to be reliably used in management of D therapy.
2. An exercise study should be performed when rest EF is N, but is unnecessary when rest EF is ABN.
3. All Pts with resting EF 45%, exclusive of other cardiac disease should have D discontinued.
4. Biopsy is useful in assessing D cardiotoxicity in patients with other possible causes of ABN. GNA.

RIGHT VENTRICULAR CARDIOMYOPATHY PRESENTING WITH RECURRENT VENTRICULAR TACHYCARDIA

D.H. FITCHETT, MB; C.G. MacArthur, MB; C.M. Oakley, MD, FACC; D.M. Krikler, MD, FACC; J.F. Goodwin, MD, FACC, Royal Postgraduate Medical School, Hammersmith Hospital, London, England.

Dilated cardiomyopathy usually presents with either left or biventricular failure, less often with arrhythmia or embolism. We describe 14 patients with severe right ventricular dilatation in whom there was apparent sparing of the left ventricle. Eight patients were male and six female, age range six to 55 years, average 28. Ventricular tachycardia was the cause of referral in seven patients, none of whom had other symptoms or signs of cardiac abnormality. Only five patients had clinical heart failure. The ECG suggested right ventricular abnormality in 12 patients and two had sino atrial disease. Echocardiography revealed marked dilatation of the right ventricle with a normal left ventricle and right ventricular angiography showed marked dilatation but only two patients showed any detectable abnormality of left ventricular function. Ventricular arrhythmias were documented in eight patients with appearances suggesting an origin in the right ventricle confirmed by electrophysiological studies in three. Six patients died, three suddenly and three with severe heart failure. Autopsy in three patients showed extreme dilatation of the right heart chambers and normal appearance of the left heart chambers although histological abnormality was found in both ventricles. It is suggested that the spectrum of dilated cardiomyopathy includes apparently isolated right ventricular dysfunction and should be suspected particularly when ventricular tachycardia is associated with T wave inversion in right-sided ECG leads.

MORPHOLOGIC BASIS FOR ELECTROCARDIOGRAPHIC EVIDENCE OF CONDUCTION SYSTEM INVOLVEMENT IN DUCHENNE'S MUSCULAR DYSTROPHY (DMD)

Shyamal K. Sanyal, F.A.C.C., Warren W. Johnson, M.D., Saroja Bharati, M.D., and Maurice Lev, M.D. St. Jude Children's Research Hospital, Memphis, Tennessee and Hecton Institute, Chicago, Illinois.

Twelve-lead electrocardiograms were analyzed in 50 boys, 5 to 18 years of age, who had clinical, biochemical and muscle biopsy evidence of DMD. Cardiac conduction system abnormalities were noted in 27 patients (54%). Intra-atrial conduction abnormalities were most common and included: abnormal PV_1 index in 14 patients, a short P-R interval in 11 and coronary sinus rhythm in 2. Intraventricular conduction abnormalities were noted in 5 patients: right bundle branch block in 2, left anterior hemiblock in 2 and bifascicular block in 1. First-degreee atrioventricular block was seen in 1 patient. Seven patients had more than one type of conduction defect. Serial follow-up observations disclosed that the conduction abnormalities were progressive.

To determine the genesis of these EKG abnormalities, we studied systematically, the morphology of the cardiac conduction system in 4 patients with DMD. In each instance, within 1-2 hours of death, hearts were perfused at 4°C for four hours either with 2.5 glutaraldehyde (2 hearts) or with 10% formalin (2 hearts). In contrast to the heart of sex-matched, normal control subject, each DMD heart showed multifocal areas of degenerative changes characterized by vacuolization, fatty infiltration, and nuclear pyknosis. Other changes included variation in size and staining of myofibers, splitting and loss of myofibers and moderate-to-severe fibrosis. These dystrophic changes at the cellular level were similar in each patient and involved, with varying degrees of severeity, sino-atrial node, atrial preferential pathways, atrioventricular node, bundle of His and subendocardial as well as intraventricular right and left bundle branches.

Our observations indicate a high prevalence of cardiac conduction abnormalities in patients with DMD. Morphologic observations establish that the EKG abnormalities result from dystrophic involvement of the cardiac conduction system in these patients.

CARDIAC EFFECTS OF PLASMA FROM PATIENTS WITH GRAVES' DISEASE

Anthony Nathan,MB;Paresh Dandona,DPhil;Donald Longmore,MB. St.Bartholomew's Hospital,London,England

Patients(pts) with cardiomyopathies(CM) have a higher than expected incidence of thyrotoxicosis.CM may occur during a euthyroid phase.The possibility that plasma rich in thyroid stimulating immunoglobulins(TSI) may have a role in the pathogenesis of such CM has been investigated as TSI are recognised to have extrathyroidal effects. Plasma from 3 patients(A,B,and C) with Graves' disease, and from controls,were tested on intact fetal mouse hearts in organ culture.Each of the pts had become euthyroid but all had fulminant exophthalmos.TSI levels were elevated in pts plasma,but not in the controls.Electrolytes and thyroid hormone levels were normal in all the pts and controls.Test plasma was added to aliquots of tissue culture medium.40 hearts were used in each experiment,20 for the pts plasma,and 20 for the controls.Plasma from each of the 3 pts caused a significant increase in mean heart rate in comparison with controls(A:131,control: 83;$p<0.001$, B:212,control:109;$p<0.001$, C:181,control:97; $p<0.01$).Survival in hearts incubated with pts plasma was significantly reduced in comparison with control(50% survival:pts-15.5 days,control-27 days).In addition,plasma from patient A obtained after 4 days of therapeutic plasmaphoresis(when TSI levels were significantly reduced) had no effect on either heart rate or survival when compared with controls.

These results suggest that a plasma factor present in these patients exerts a deleterious effect on cardiac tissue causing initial stimulation(with an increase in heart rate) followed by premature death.These effects may be caused by TSI,which interestingly often persist for years after a euthyroid state has been achieved.

REDUCTION OF MYOCARDIAL FIBROSIS BY EARLY METHYL PREDNISONE OR IBUPROFEN ADMINISTRATION IN EXPERIMENTAL RADIATION INDUCED HEART DISEASE

William C. Reeves, MD, FACC; David Cunningham, MD; Joseph Schwiter MD; Arthur Abt, MD; Sonia Skarlatos; Mary Ann Wood; Larry Whitesell

The ability of methyl prednisone (MP) and ibuprofen (IB) to reduce the severity of the late stage of radiation-induced heart disease (RIHD) was assessed in 57 New Zealand white rabbits. Thirteen rabbits served as unirradiated controls. (Group C) Fifteen rabbits in group A (MP) and 15 rabbits in group B (IB) received intravenous drugs before and shortly after cardiac irradiation. No drug was administered to 14 irradiated rabbits in the final group. All 15 rabbits in group A lived for 100 days. Thirteen of the 15 rabbits in group B lived for 100 days. Only 7 of the 14 rabbits in the untreated irradiated group lived for 100 days. Longevity was significantly improved in groups A ($p<.01$) and B ($p<.05$) when compared to the untreated irradiated group. Surviving animals were sacrificed at 100 days post irradiation. Myocardial fibrosis was evident in all irradiated groups by microscopic examination. Quantitation of the fibrosis was achieved by determination of myocardial hydroxproline content (MHP) in 13 untreated irradiated rabbits and in 13 rabbits each in groups A, B, and C. MHP was significantly increased in the untreated irradiated group (72.0 ± 5.3 mg/gram dry tissue) (Mean $\pm$ SEM) compared with group C (34.4 ± 2.2) ($p<.01$). MHP was significantly reduced in groups A (48.7 ± 6.2) ($p<.05$) and B (49.1 ± 7.1) ($p<.01$) when compared to the untreated irradiated group. Early MP or IB administration retards the development of myocardial fibrosis and improves survival in this experimental model of RIHD.

MONDAY, MARCH 16, 1981
PM
ECHOCARDIOGRAPHY: MYOCARDIAL ISCHEMIA & INFARCTION
2:00-3:30

QUANTITATIVE REGIONAL MYOCARDIAL PERFUSION SCANNING WITH CONTRACT ECHOCARDIOGRAPHY

William J. Bommer, MD, FACC; Julia Rasor, MS; Glenn Tickner, MS; Patricia Takeda, MD; Larry Miller, PhD; Garrett Lee, MD; Dean T. Mason, MD, FACC; Anthony N. DeMaria, MD, FACC, University of California, Davis and Sunnyvale, California

Current echocardiography techniques provide no quantitative information about myocardial perfusion. Thus we developed a new method for quantitating myocardial perfusion in the presence of coronary artery obstruction. During two-dimensional echocardiographic imaging, we injected a suspension of stabilized microbubbles (10-30 μ) into the left ventricle (LV) and coronary arteries (COR) of 7 dogs before and after obstruction of the left anterior descending branch (LAD). Using echo-videodensitometry, perfusion in selected areas of myocardium could be monitored by recording contrast curves and measuring both peak contrast effect and the time to 50% disappearance of peak effect (DT-50). In normal COR, selective left coronary injections produced uniformly bright opacification of the entire myocardial circumference. After LAD obstruction, septal myocardial opacification was significantly reduced (mean reduction of peak contrast effect 90%) compared to the LV free wall. Normal COR perfusion curves showed a significantly prolonged DT-50 (10.5 sec), when compared with LV chamber curves (DT-50 = 3 sec, $p<.01$). Although the peak contrast effect in ischemic tissue was reduced, DT-50 of ischemic areas was unexpectedly shorter than normal (7 versus 10.5 sec, $p<.05$). Thus, echo-videodensitometry of contrast myocardial perfusion scans yields quantitative curves which differentiated normal from ischemic muscle. The accelerated DT-50 seen in association with decreased peak contrast effect in ischemic muscle may reflect a reduced microbubble to vessel diameter ratio as well as reduced flow.

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC ASSESSMENT OF WALL THINNING AND ITS RELATION TO PERFUSION DURING GRADED CORONARY STENOSIS.

Natesa Pandian, MD; Richard Kerber, MD, FACC, CV Cent, Univ of Iowa Hosp, Iowa City, Iowa.

The utility of two-dimensional echocardiography (2DE) in detecting myocardial ischemia with varying degrees of coronary stenosis (CS) without complete occlusion is not established, and the change in perfusion accompanying 2DE wall thinning in CS has not been defined. To study this, we created circumflex CS in 25 dogs. Coronary blood flow (CBF) was measured by electromagnetic flow probes and myocardial perfusion (P) by radioactive microspheres. 70% CS abolished reactive hyperemia; 90% CS reduced CBF by half. To induce ischemia, isoproterenol (Iso) and acute aortic constriction (AC) were added to CS. Ischemia was defined as systolic wall thinning by ultrasonic sonomicrometers and by 2DE. From 2DE short-axis left ventricular images, the % systolic thickening of 12 equidistant wall radii was analyzed. Control wall thickening was 34±SD11% (range 5 to 100%). Systolic thinning was never seen with 2DE or sonomicrometers in control state or with 70% or 90% CS alone, nor was P significantly reduced with CS alone. When Iso and AC were superimposed on 90% CS, segmental thinning occurred in all dogs, with thinning of individual radii ranging from -5 to -53%. In the radii opposite the ischemic segments, thickening increased from 33±12% control to 81±39% ($p<.01$). Whenever thinning was detected severe hypoperfusion was inevitably present, with P falling from 116±29 ml/100g/min control to 28±16 ml/100g/min during thinning ($p<.01$). Conclusion: Even severe CS may not cause decreased P at rest, and 2DE in this case shows no wall thinning. Interventions which cause hypoperfusion produce ischemia and wall thinning in the involved area, and exaggerate thickening in the opposite nonischemic myocardium. This permits 2DE detection of severe CS; systolic thinning always signified perfusion <25% of control.

HIGH FREQUENCY EPICARDIAL ECHO MAPPING OF SEGMENTAL MYOCARDIAL PERFORMANCE AT MULTIPLE SITES ON RIGHT AND LEFT VENTRICLES

Mariell Likoff, Nathaniel Reichek, John Macoviak, Alden Harken, FACC, Martin St. John Sutton, Ali Muhammed, Ted Plappert and John A. Kastor, University of Pennsylvania, Philadelphia, PA.

To develop a new method for analysis of segmental myocardial function, 7.5 mHz transducers (resolution 0.2mm) were used to record epicardial echograms at multiple sites on both ventricles in 7 open-chest dogs before, during and after ischemia produced by brief coronary occlusions; and in 6 men with 2 or 3 vessel coronary disease during coronary surgery. Plots of myocardial thickness(T) and its normalized derivative dT/dtT (an analogue of velocity of fiber shortening) were compared to strain gauge recordings in dogs. Dog left and right ventricular normal peak systolic(PS, 7.3±1.8 vs 6.8±2.3) and diastolic(PD, -6.0±1.4 vs -6.6±3.2) dT/dtT were similar and occurred early in systole and diastole, respectively. Ischemia led to prompt fall and delay in PS and PD dT/dtT (-3.0T/sec, $p<.001$; +1.4, $p<.02$; n=17) with paradoxical systolic thinning in central ischemic zones. Echograms were more sensitive to ischemia than strain gauge, but as specific. Reperfusion promptly corrected PD dT/dtT but PS dT/dtT improved slowly and incompletely. Pre-bypass recordings in man demonstrated marked heterogeneity of myocardial function even in areas without transmural infarction or ventriculographic abnormality. The echo method is simple, rapid, atraumatic, has excellent spatial resolution and permits more extensive mapping than strain gauge. We conclude that epicardial echo mapping can improve analysis of segmental myocardial function and is readily applicable to man.

CROSS-SECTIONAL ULTRASONIC IMAGING OF THE CORONARY ARTERIES (CA's) IN OPEN CHESTED HUMANS; THE EVALUATION OF CORONARY ATHERSCLEROTIC LESIONS (ACL) AT SURGERY.

David J.Sahn, MD, FACC; Brian Barratt-Boyes, MD, Ken Graham, MD, Alan Kerr, MD, Trevor Agnew, MD, Antony Roche, MD, Peter Brandt, MB, ChB, Univ. of Ariz. Health Sci. Ctr., Tucson and Cardiosurgical Unit, Green Lane Hosp., Auckland, N.Z.

Because the location of angiographically demonstrated ACL at surgery is inexact, we have developed a new ultrasonic method for imaging CA's in open chested humans during surgery. A 9mHz electronically focussed water path ultrasound scanner was used to image the CA's on three anaesthetised open chested sheep. The images were compared to anatomic observations and measurements. CA's and coronary veins could be identified in longitudinal as well as transverse sections. In 10 human subjects, the ultrasound probe was gas sterilised and placed directly on the beating heart. The right (R)CA orifice was imaged by placing the probe over the aorta and the RCA could be followed in the atrioventricular sulcus. The left (L)CA orifice was imaged through the pulmonary artery and the main LCA, the proximal L circumflex and L anterior descending could be imaged. The distal L anterior descending CA was imaged on the anterior surface of the heart in the inter-ventricular sulcus. These vessels could be studied with the heart beating or during cardiopulmonary bypass. The distal L circumflex could be imaged only on bypass with the heart rotated apex up. Using this method compared to angiography and surgical observations, we have imaged normal CA's as well as ACL in the proximal R, mid-R, proximal L main and L anterior descending CA's; in two cases confirming the presence or absence of additional occlusive ACL's in CA's poorly filled angiographically. This new method allows the intra-operative verification and localisation of ACL and aids in the accurate placement of saphenous vein bypass grafts.

DISCRETE INTRAMURAL SONOLUCENCY: A NEW ECHOCARDIOGRAPHIC FINDING IN ACUTE MYOCARDIAL INFARCTION.
J.A. Werner, M.D., FACC, S.M. Speck, M.D., H.L. Greene, M.D., FACC, C.L. Janko, B.W. Gross, M.D. Harborview Medical Center, University of Washington, Seattle, Washington.
Pathological studies have suggested evolutionary changes within myocardium during acute myocardial infarction (AMI) including edema, hemmorhage and geometrical changes occurring over hours to days. To determine if such changes may be detected non-invasively early in the clinical course, we performed two-dimensional echocardiography (2DE) within 24 hours of admission on 27 pts with documented AMI by cardiac enzymes and EKG. Discrete areas of intramural sonolucency (DIS) were seen on 2DE corresponding to the EKG area of infarction in 10/27 (37%) pts - all with involvement of the anterior wall.

Follow-up studies at 48 hours, available in 5 pts, continued to show the abnormality in 4/5 pts and was equivocal in one. Six of the 10 pts with DIS died in hospital compared to 2/17 pts without DIS ($p<.03$). Autopsy performed in 3/6 fatal cases with DIS demonstrated myocardial rupture in 2/3 and extensive infarction with edema and hemmorhage in the remaining pt - all corresponding to the abnormal area (DIS) identified on the 2DE. Cardiac enzymes were markedly elevated in all pts and did not distinguish pts with DIS or subsequent death. We conclude that DIS represents edema and hemmorhage in the zone of acute infarction and when identified echocardiographically, suggests a poor clinical outcome.

CROSS-SECTIONAL ECHOCARDIOGRAPHY IN THE EARLY DETECTION OF ACUTE MYOCARDIAL ISCHAEMIA AND INFARCTION.
K. Daly, M.R.C.P.I., M. Monaghan, MSc, G. Jackson, M.R.C.P Cardiac Department, King's College Hospital, London, U.K.

Fifty patients (pts) with suspected diagnosis of acute myocardial infarction (M.I.) had cross-sectional echocardiographic studies carried out on admission to the coronary care unit and forty eight hours later. None had a past history of M.I. or hypertension. The LV wall was divided into 11 segments, and segmental wall motion defined as normal, hypokinetic, akinetic or dyskinetic. The degree of asynergy calculated was expressed as a percentage (normal 0% total dysynergy 100%) and compared with creatine phosphokinase (CPK) level and 12 lead ECG at the time of study.
M.I. was later confirmed in 40 pts on the basis of elevated CPK and/or ECG. Elevated percentage asynergy was present in 39 on admission, and in the remaining one at 48 hrs. M.I. could not be diagnosed in 17 of these on admission - 8 pts had normal CPK (134-26 i.u./L) rising to 1012 i.u./L at 48 hours, and 9 pts had non-diagnostic ECG patterns. All had evidence of L.V. wall motion abnormality (% asynergy score 23 on admission rising to 33 at 48 hours) 10 pts did not suffer M.I. 8 had normal echocardiograms. The remaining 2, whose ECGs showed acute ischaemic patterns had LV asynergy (% score 15) on admission- the echocardiograms reverted to normal after the acute ischaemic episode.
These findings indicate that cross-sectional echocardiography is a sensitive method of early detection of acute myocardial ischaemia and infarction in pts who have not had prior M.I. It is particularly of value when initial CPK values and ECG patterns are not diagnostic.

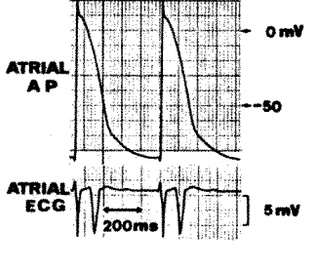
MONDAY, MARCH 16, 1981
PM
THE SINUS NODE AND ATRIUM
2:00-3:30

EFFECT OF OVERDRIVE PACING ON ELECTRICALLY AND NEUROLOGICALLY ISOLATED SINUS NODE IN OTHERWISE INTACT DOGS
Florence Chan MD, Jerry Gliklich MD, Brian Hoffman MD,FACC Columbia University, New York, N.Y.

Sinus node (SN) function is evaluated by atrial overdrive (OD) and atrial premature stimulation. Interpretation is difficult because SN activity is not directly recorded and reflex effects make unknown contributions to observed changes in atrial rhythm and rate. We have prepared isolated sinus nodes (sinus node islands SNI) in chronically instrumented dogs by a circumferential incision as described by Sealy. Electrodes were attached to the epicardium to record the SN electrograms. Pacing electrodes were attached to the atrial remnants. Isolation of the SNI from the atrium was demonstrated by the independence of the sinus and atrial rhythm and the ability to pace the SNI and atrium independently. Neurologic isolation of the SNI during the first 2 weeks was shown by a constant sinus rate during cervical vagal stimulation. Effects of OD and premature stimulation were compared for SNI and intact hearts. The SN electrogram permitted identification of SN capture during OD. In intact hearts OD at cycle lengths (CL) 800-400 msec caused marked prolongation of the return cycles. A progressive decrease in return CL was noted at pacing CL of 400-250 msec. Finally, at quite short CL, post-OD acceleration was seen. In the SNI, increasing OD suppression was again demonstrated at 600-300 msec CL. At CL of 300-180 msec, the extent of OD suppression decreased as the pacing rate increased. Post-OD acceleration was not seen.
We concluded that the SNI offered a good method of studying the response of SN to OD in the absence of reflex effects. The varying degree of suppression in response to different rates of stimulation is unrelated to neurotransmitter effects.

A NEW METHOD OF RECORDING TRANSMEMBRANE ACTION POTENTIAL FROM ATRIA OF IN SITU HEART
Toshio Akiyama, MD, FACC; Winshih Chang; Jay Luft, University of Rochester Medical Center, Rochester, NY

Cardiac motion interferes with in situ action potential (AP) recordings. We have recently developed a motion compensated micropipette holder (MCMH) which senses cardiac motion and lifts and lowers a micropipette of Ling-Gerard type and supporting apparatus in synchrony with heart beat. The MCMH was applied to right atrial appendage of 8 open-chest fluothane-anesthetized dogs. AP of a single subepicardial cell was successfully recorded in all 8 dogs (see Figure). Withdrawal of micropipette into a thin film of Tyrode's solution covering the epicardial surface gave a zero reference potential and allowed accurate measurement of resting and overshoot potentials. Characteristics (mean ± SEM) of AP of subepicardial cells of right atrial appendage at serum Na 142 and K 4.2 mEq/L are: heart rate 117 ± 7 beats/min, resting potential -80.8 ± 2.0 mV, overshoot potential 18.6 ± 2.1, upstroke dV/dt 20.8 ± 0.7 V/sec, 90% AP duration 257 ± 8 msec. In conclusion, the MCMH, by moving synchronously with the heart, allows reliable AP recording from atrial cells of the beating heart in situ, and may become an invaluable tool to assess the effects of drugs on atrial cells and to accurately measure sino-atrial conduction of the in situ heart in animals.



ELECTROPHYSIOLOGY OF THE CANINE SINUS NODE DURING CARDIOPULMONARY BYPASS: TECHNIQUE FOR LOCALIZATION AND RESPONSE TO COLD CARDIOPLEGIA. Jerry Gliklich, MD, Florence Chan, MD, Brian Hoffman, MD,FACC. Columbia University, New York New York.

High gain low frequency unipolar electrograms were recorded with ring or plaque electrodes from the epicardial surface of the heart in dogs undergoing cardiopulmonary bypass. The pacemaking region of the sinus node (PRSN) was defined as the site where the sinus node electrogram (SNE) revealed both primary negativity and an upstroke slope. In general, the PRSN was found on the RA, near the superior vena cava along the axis between the cavae. In some animals the PRSN was midway between the cavae. The core temperature (T) was decreased to 30°C prior to aortic cross-clamp and injection of cardioplegic solution. ([K]=30mM, T=4°C). Administration of cardioplegia rapidly produced slowing of ventricular conduction followed by ventricular standstill. Atrial activity was attenuated more slowly and SN potentials generally persisted longest. During quiescence, ventricular T=10-18°C and atrial T was 4-8°C higher. During cross-clamp the SNE occasionally revealed spontaneous rythmic SN activity, with a superimposed more rapid deflection corresponding to atrial activity. Phase 4 depolarization was clearly seen in these complexes and patterns of SN reentry were noted. As the core was warmed to 30°C prior to release of the aortic cross-clamp, SN activity invariably returned. In conclusion, it is possible to electrophysiologically localize the PRSN on the epicardium during open heart surgery, thereby possibly preventing SN damage in certain situations. In addition, the SN pacemaker appears to be more K and cold resistant than the atrium or ventricle.

EXCELLULAR RECORDING OF DIASTOLIC SLOPE IN DOGS AND HUMANS WITH HIS BUNDLE RHYTHMS •
Robert J. Hariman, MD, FACC; Chia-Maou Chen, MD, Sun H. Lau, MD; Anthony N. Damato, MD, Department of Cardiology, U.S. Public Health Service Hospital, Staten Island, N.Y.

His bundle (HB) rhythms were induced in 8 open chest dogs by exclusion of the sinus node. Recorded were bipolar atrial electrograms (E) using plaque electrodes sutured on the right atrial appendage and bipolar HB E using plunge electrodes. Unipolar HB E were recorded (time constant 0.1 sec, amplification 100 to 200 μV/cm) using the plunge electrodes paired with an indifferent plaque electrode on the superior vena cava. HB rhythms fulfilled the following criteria: During HB rhythms, a bipolar HB deflection preceded the ventricular complexes, which had QRS configuration and H-V interval identical to those during sinus rhythm or atrial pacing. The unipolar HB E showed negatively directed diastolic slope (DS), with a dV/dt of 0.1-5mV/sec,preceding the bipolar HB deflection. Vagal stimulation and/or I.V acetylcholine (10 mg) injection produced slowing of HB rhythms associated with a decrease in the dV/dt of DS. Similarly, overdrive suppression following atrial pacing was accompanied by a decrease in the dV/dt of DS. The responses of DS to vagal stimulation, acetylcholine and atrial pacing, which are similar to those of phase 4 depolarization, demonstrate that DS truly represents the pacemaker activity in the HB area. In one patient with a suspected HB rhythm, similar DS was recorded using an electrode catheter in the HB area paired with an indifferent electrode catheter in the superior vena cava at similar time constant and amplification. These results are important in the localization and characterization of abnormal impulse formation in the in vivo heart.

SINUS NODE EXCISION - A STUDY OF ATRIAL SUBSIDIARY PACEMAKERS - A CANINE MODEL OF THE SICK SINUS SYNDROME
John F. Moran, MD, FACC; Lynn Rinkema, BS, Walter C. Randall, PhD, FACC; Rolf M. Gunnar, MD, FACC, Loyola University Medical Center, Maywood, Il

Symptoms in the sick sinus syndrome are caused by dysfunction of the sinus node as well as failure of subsidiary pacemakers. Normal subsidiary escape pacemakers would potentially allow patients to remain asymptomatic. Dogs were surgically instrumented with high and low right atrial and left atrial electrodes. Later these animals were studied while conscious with overdrive atrial pacing and the atrial extrastimulus technique at two different drive cycles. Leads I, II, III and four atrial electrograms were recorded. Digoxin (0.05mg/Kg), propranolol (0.5mg/Kg) and atropine (0.1mg/Kg) were administered and the pacing study repeated. Sinus node recovery time averaged 900 mSec and shortened with faster pacing rates. Sinoatrial conduction time averaged 72 mSec. The sinus node was then surgically removed and the pacing studies with drugs were repeated. All studies were completed within 2 weeks in any single dog. Overdrive atrial pacing caused marked suppression of all subsidiary pacemakers with recovery times in the range of 4,000 to 10,000 mSec. Near syncope was frequently observed. The atrial extrastimulus technique caused marked suppression of the subsidiary atrial pacemakers. Propranolol and Digoxin lengthened this suppression and atropine shortened it. If the conduction time was calculated on those cycles demonstrating reset, it averaged 74 mSec. Atrial flutter and tachycardia were frequently induced. Pacemakers shifted from high to low activation and vice-versa. Conclusions: Sinus node excision allows evaluation of subsidiary pacemakers in chronic canine models. These pacemakers are initially very unstable and demonstrate marked suppression to overdrive or atrial extrastimuli.

EFFECTS OF $[K+]_o$ ON MEMBRANE POTENTIAL, DELAYED AFTERDEPOLARIZATIONS AND TRIGGERED ACTIVITY IN ATRIAL FIBERS OF THE CANINE CORONARY SINUS
Berthold Henning, M.D. and Andrew L. Wit, Ph.D., College of Physicians and Surgeons of Columbia University, New York, N.Y.

Delayed afterdepolarizations (DAD's) in fibers in the coronary sinus can reach threshold in the presence of catecholamines and result in rhythmic activity that may cause arrhythmias. Since $[K+]_o$ in coronary sinus blood may vary over a wide range, we investigated the effects of $[K+]_o$ (2.7 - 10 mM) on transmembrane potentials of atrial fibers in small coronary sinus preparations (2 mm long, 40-100μ in diameter) superfused in a fast flow system. DAD's with amplitudes of 5 mV or less followed action potentials stimulated at cycle lengths (CL's) of 10,000-5,000 msec when the level of resting membrane potential (RMP) was high (-80 to -99 mV) in superfusates containing 0.01 - 0.25μg/ml epinephrine and 2.7 mM $[K+]_o$. Triggered activity occurred when stimulus CL was sufficiently decreased. Exposure of the preparation to 4,6,8 and 10 mM $[K+]_o$ decreased resting membrane potential. DAD amplitudes increased, reaching a maximum of 10-20 mV at membrane potentials in the range of -60 to -50 mV, when the $[K+]_o$ was less than 8 mM. Triggered activity occurred at longer stimulus CL's. This suggests that the amplitude of coronary sinus DAD's are voltage dependent. At 8 to 10 mM $[K+]_o$ DAD amplitudes were reduced at all levels of membrane potential suggesting that the increase in membrane conductance which probably occurs at the higher $[K+]_o$ prevents the voltage dependent increase in DAD amplitude. Nevertheless, triggered activity was still easier to induce, probably because of the decreased difference between RMP and threshold potential. Therefore, an increase in coronary sinus blood [K+] should enhance the occurrence of triggered arrhythmias.

MONDAY, MARCH 16, 1981
PM
PHARMACOLOGY: CALCIUM ANTAGONISTS II
4:00-5:30

RELATIONSHIP BETWEEN PHARMACODYNAMICS AND MYOCARDIAL CONCENTRATION OF VERAPAMIL

Deborah L. Keefe, MD; Sandra R. Harapat, BS; Robert E. Kates, PhD, Division of Cardiology, Stanford University Medical Center, Stanford, CA.

Plasma drug concentrations are often measured to predict drug effect and avoid toxicity. The use of plasma levels is predicated on the assumption that they are in equilibrium with effector site levels, however the relationship between plasma and actual tissue concentrations at effector sites is not well understood. The relationship between the concentration of verapamil (V) in the plasma and in myocardium and drug effect as measured by %PR interval prolongation (%PRΔ) was studied in open-chested anesthetized dogs. Blood samples, myocardial biopsies, lead II ECG recordings, and arterial pressure tracings were obtained before and at 10,20,30,40,60,80,100,120,150, 180,210,240 and 300 minutes after the intravenous administration of V (0.5mg/kg) over 5 minutes. Verapamil concentrations in plasma and myocardium were measured by high pressure liquid chromatography. Verapamil administration resulted in a marked PR interval prolongation (average maximum 70 ± 30%). Two of the 6 dogs developed transient 2:1 AV block at levels of V above 3.65μg/gm of tissue in myocardium and 168ng/ml in plasma. The drug was concentrated in the myocardium reaching an average peak of 3.15 ± 0.87μg/gm of tissue which was more than 10 times the simultaneous mean plasma level of 245 ± 86ng/ml. The %PRΔ correlated well with myocardial concentration ($p<.001$). Myocardial kinetics were similar to plasma kinetics although the correlation of %PRΔ with myocardial level was somewhat better than that for plasma level. Both myocardial and plasma V levels correlated well with the degree of atrio-ventricular block and plasma levels of V are predictive of drug effect.

CONCENTRATION DEPENDENT HEART RATE SUPPRESSION WITH VERAPAMIL

Janice B. Schwartz, MD; Deborah Keefe, MD; Flora Peters, RN; Robert Kates, PhD; Donald C. Harrison, MD, Stanford University, Stanford, California

The relationship between serum Verapamil (V) concentration and heart rate suppression was studied in 5 patients with chronic atrial fibrillation. Following the determination of V pharmacokinetics in each patient using a 3 compartment model, V infusions were given to reach 4 steady-state levels: 15 ng/ml, 30 ng/ml, 60 ng/ml, and 120 ng/ml. At baseline and at each steady-state level, resting heart rate and heart rate after dumbbell exercise, and after sublingual nitroglycerin (NTG) was determined.

	Verapamil Concentration (ng/ml)				
	0	15	30	60	120
Resting Heart Rate	104	75	73	66	62
% Reduction					
Resting Heart Rate		24%	29%	34%	40%
$\bar{p}$ Dumbbell		20%	23%	30%	37%
$\bar{p}$ NTG		24%	25%	33%	42%

Serum concentrations of 15 or 30 ng/ml V produced significant ($p<.02$) suppression of resting, exercise and NTG stimulated heart rate. Increasing the V concentration to 60 or 120 ng/ml produced a further + significant ($p<.05$) decrease in resting, exercise and NTG stimulated heart rate. There were no significant differences between the effects of 15 vs. 30 or 60 vs. 120 ng/ml V.

Conclusion:

The serum concentration of Verapamil relates to the magnitude of suppression of resting, exercise, and NTG stimulated heart rates and can provide a guideline to clinical effects.

DIFFERING EFFECTS OF VERAPAMIL RELATIVE TO VARYING LEVELS OF MYOCARDIAL PERFORMANCE IN PATIENTS WITH CORONARY ARTERY DISEASE

Christopher Y.C. Chew, MD; Harvey S. Hecht, MD, FACC; Stephen Schnugg, MD; James Hopkins, BS; Bramah N. Singh, MD, FACC, Wadsworth VA Hospital, Los Angeles, Ca.

Verapamil (V) interferes with EC coupling in cardiac muscle and may exert significant negative inotropism. Accordingly, the intravenous effects of Verapamil (0.145 mg/kg over 2 mins and 0.005 mg/kg infusion) on left ventricular radionuclide ejection fraction (EF) and hemodynamics were evaluated in 25 pts with coronary artery disease including 8 with acute myocardial infarction. The data (M±S.D.) for pts (n=22) with PCW <18 mmHg are:

	C	V	P
HR	74±10	77±11	<0.05
BP	98±12	83±12	<0.001
PCW	10±3	12±3	<0.001
SI	41±10	44±10	<0.01
SVR	1424±320	1104±304	<0.001
EF(%)	52±18	56±9	NS

(C=pre-V; PCW=mean pulmonary capillary wedge; SI=stroke volume index; SVR=systemic vascular resistance; N.S.=not significant. Three patients with heart failure (PCW >20 mmHg; EF 26±8%) deteriorated clinically with an increase in PCW 26±5 to 33±3, a decrease in SI 33±5 to 28±5 with the development of pulmonary hypertension.

Conclusion: 1) Verapamil in coronary artery disease pts with PCW <18 mmHg exerts minimal depression on myocardial function; 2) in patients with heart failure (PCW >20 mmHg) Verapamil causes further deterioration and thus should be used with great caution.

EFFECT OF VERAPAMIL ON LEFT VENTRICULAR FUNCTION: RANDOMIZED, PLACEBO-CONTROLLED STUDY

Ronald E. Vlietstra, MD, FACC; Maria A. Farias, PhD; Robert L. Frye, MD, FACC; Hugh C. Smith, MD, FACC; Erik L. Ritman, MD, Mayo Clinic, Rochester, MN.

At cardiac catheterization, 25 pt were allocated by a random, double-blind method to intervention with placebo (saline) or verapamil (0.2 mg/kg total by bolus and 10-min infusion). Control and immediate postintervention hemodynamic measurements and left ventriculography allowed estimation of the values shown in the table below (MAP = mean arterial pressure; $+\bar{p}$ dTw/dt = peak rate of anterior wall systolic thickening; $-\bar{p}$ dTw/dt = peak rate of anterior wall diastolic thinning). Of the 25 pt (24 males, 1 female), 3, 3, 10, and 9 had 0, 1, 2, and 3 vessels narrowed ≥50%, respectively.

	Placebo (n=12)		Verapamil (n=13)*	
	Before	After	Before	After
Heart rate, beats/min	68	70	68	70
MAP, mm Hg	103	109	105	89†
CI, liters/min/m^2	2.9	2.9	2.8	3.1†
LV end-diastolic pressure, mm Hg	17	19	16	19
End-diastolic volume index, ml/m^2	91	89	94	102†
End-systolic volume index, ml/m^2	37	34	39	41
Ejection fraction, %	60	62	58	59
$+\bar{p}$ dTw/dt, mm/sec	35	35	27	25
$-\bar{p}$ dTw/dt, mm/sec	34	33	30	29

*For ventriculogram data, n=9. †$P<0.01$, paired t test. Hemiaxial shortening, for placebo and verapamil groups, decreased >10% in 4/48 and 8/48 segments and increased >10% in 8/48 and 9/48 segments, respectively ($\chi^2=1.52$, $P>0.1$). This statistical analysis indicates that verapamil lowers MAP, raises CI, and has little effect on LV function.

SUSTAINED BENEFICIAL EFFECT OF NIFEDIPINE IN CHRONIC REFRACTORY HEART FAILURE.

Fulvio Bellocci,M.D.;Gerardo Ansalone,M.D.;Enrico Scabbia,M.D.;Vincenzo Affinito,M.D.;Pietro Santarelli,M.D.; Franco Loperfido,M.D.;Paolo Zecchi,M.D.
Catholic University of Sacred Heart,Rome,Italy.

NIFEDIPINE (N) is a calcium antagonist drug which induces vascular smooth muscle relaxation. We have studied acute and chronic hemodynamic effects of N in 8 patients(pts) with refractory congestive heart failure(CHF)to evaluate the clinical use of N as a ventricular unloading agent. All pts had idiopathic cardiomyopathy and were in NYHA functional class III or IV. Measurements were recorded before and after the 20 mg oral dose of N and were repeated after 2 months of oral N(20 mg every 6 hours). Measurements included:heart rate(HR),bpm;mean blood pressure(MBP),mmHg;left ventricular filling pressure(LVFP),mmHg; cardiac index(CI),L/min/M^2;stroke volume index(SVI), ml/beat/M^2;total systemic vascular resistance(TSVR),dsc^{-5}; HR x systolic BP product(MVO_2 index). "p < 0.01 or below.

	HR	MBP	LVFP	CI	SVI	TSVR	MVO_2
Control	81	90	26	1.9	23	2250	10530
Initial	87	73"	19"	3"	34"	1250"	10005
2Months	84	76"	20"	3.1"	37"	1100"	9912

All pts had symptomatic improvement of at least one NYHA functional class.Thus,we conclude that N acutely raises CI and SVI and lowers LVFP and TSVR,and the hemodynamic responses are still evident following long-term therapy. These data support the use of N as an effective unloading agent for chronic therapy of CHF.

MONDAY, MARCH 16, 1981
PM
CORONARY ARTERY DISEASE: SELECTED TOPICS
4:00-5:30

ANGIOGRAPHIC DYE RELAXES CANINE CORONARY ARTERY BY A NON-OSMOTIC MECHANISM

Karen I. Bentley, BS; Malcolm Clark, Philip D. Henry, MD, FACC. Washington University, St. Louis, MO.

During coronary arteriography the coronary vessels are briefly exposed to very high concentrations of angiographic dye. To characterize the effects of Renografin 76 (Na-diatrizoate, 1689 mosmol/liter) on coronary vasomotion, isolated canine coronary arteries (n=35) were mounted in a myograph for the recording of isometric tension, and exposed to oxygenated Krebs buffer containing graded doses of dye or iso-osmotic solutions of NaCl, Na_2SO_4, Na-tartrate, Na-ascorbate, KCl, and mannitol. Low doses of dye (< 3 ml/100 ml Krebs) evoked strong, sustained relaxations, and largely suppressed contractions elicited by 10^{-6}M ergonovine. High doses (4-16 ml/100 ml) produced dose-dependent spasms which were completely reversible upon removal of the dye. The other agents evoked no or minimal transient relaxations and acted as constrictors. The constrictor potency was KCl > dye > Na-tartrate > Na-ascorbate > mannitol > Na_2SO_4 > NaCl. Therefore, nonpermeating non-ionic solute (mannitol) and Na-salts with variously permeant anions did not mimic the effects of Na-diatrizoate. Verapamil, nifedipine, and nitroglycerin (all 10^{-6}M) relaxed contractions produced by KCl by > 80%, but reduced those induced by dye or Na-salts only by < 10%. Thus, low-dosed dye elicited relaxations by a non-osmotic mechanism, and higher doses precipitated spasms which were unresponsive to potent vasodilators. Results raise the possibility that dye may attenuate spontaneous or ergonovine-induced spasms during arteriography. Also, multiple injections or stagnant flow due to ventricular fibrillation might expose coronary smooth muscle to high concentrations and precipitate refractory spasms.

CLINICAL UTILITY OF PLASMA VERAPAMIL LEVELS IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Martin B. Leon, MD; Douglas R. Rosing, MD; Taysir M. Jaouni, MS; Henry M. Fales, PhD; Stephen E. Epstein MD, FACC; NHLBI, Bethesda, Md.

A highly sensitive, reproducible high pressure liquid chromotography assay was used to determine the importance of plasma verapamil levels (PVL) in guiding therapy of patients with hypertrophic cardiomyopathy. In 80 patients on chronic oral verapamil therapy, there was marked variability between patients in PVL for each dosage.

dose (mg/day)	240	360	480	640
mean PVL±2SD (ng/ml)	84±72	163±172	174±208	258±170

In contrast, variability in peak and trough PVL for a given patient was relatively small (verapamil peak/trough ratio for 23 patients=1.66±.07). PVL in 27 clinical responders (R), with improvement in NYHA functional class and >15% increase in exercise capacity, were not different from 15 nonresponders (NR) (R=153±11, vs NR=175±18 ng/ml; NS). Also, in 6 patients with atrial fibrillation, there was a poor correlation between PVL and decrease in ventricular response (r=0.52) after a single 80 mg verapamil tablet. Moreover, PVL in 24 patients with serious electrophysiologic or hemodynamic side effects from verapamil ranged from 30 to 540 ng/ml and the mean PVL (201 ±23 ng/ml) was no different from the R or NR.
Thus, in patients with hypertrophic cardiomyopathy on verapamil therapy 1) there is marked interpatient variability in PVL, which may be due to differences in first pass hepatic metabolism, 2) PVL are similar in R, NR, and patients with serious side effects. PVL are therefore of limited usefulness in predicting therapeutic or toxic effects in patients with hypertrophic cardiomyopathy.

DOPPLER SONES QUANTITATION OF CORONARY BLOOD FLOW IN MAN DURING DIPYRIDAMOLE CORONARY VASODILATATION

Kent L. Richards, MD, FACC; Sherman G. Sorensen, MD, FACC; Craig Hartley, PhD; William P. Dole, MD, University of Texas Health Science Center and Veterans Administration Hospital, San Antonio, Texas

We studied changes in coronary artery flow during intravenous dipyridamole (DP) induced coronary vasodilatation (0.14 mg/kg/min for 4 min) in 6 patients using a unique Sones angiographic catheter equipped with a 20 mHz pulsed doppler transducer at its tip and a transformer electrical coupler at its hub. Heart rate, intravascular pressure, coronary blood velocity, and cardiac output were measured before and after intravenous DP. Coronary artery blood flow was also measured during DP vasodilatation with handgrip and coronary angiography. Mean ±SD heart rate (HR, beats/min), blood pressure (SBP), cardiac output (CO), coronary blood flow (CBF, as KiloHz) for normal (NL) and abnormal (ABN, >50% stenosis) were:

	HR	SBP	CO	CBF/NL	CBF/ABN
CONTROL	70±12	122±24	7.1±1.8	2.1±.86	3.8±1.1
DIPYRIDAMOLE	86±13	110±17	7.7±2.7	4.1±1.7*	3.6±1.4

Handgrip failed to increase CBF in NL arteries (4.1 KHz vs 4.4 KHz). Stenotic arteries (pre and post DP) and normal arteries (post DP) demonstrated blunted hyperemic flow response to contrast arteriography (4.43 vs 4.75; normal increase 2-3.4 fold). Two normal patients failed to increase CBF with DP; both developed arterial hypotension and diastolic pressures less than 60 mmHg with DP. We conclude that 1) CBF increases in NL arteries but not ABN arteries after DP, 2) varied responses to DP may occur due to altered hemodynamics or dose response.

*p<.05

EFT VENTRICULAR RESPONSE TO EXERCISE AFTER ANTERIOR YOCARDIAL INFARCTION: • DIFFERENCES BETWEEN PATIENTS WITH INGLE AND MULTIVESSEL CORONARY ARTERY DISEASE.
rthur T.H. Tan MB, Norman Sadick MB, Roger F. Uren MB hillip J. Harris MB FACC, David T. Kelly MB FACC. allstrom Institute of Cardiology, Sydney, Australia.

Patients with single or multivessel disease may have mpaired LV function at rest after anterior transmural yocardial infarction. To determine whether the LV response to exercise was different in these two groups, 26 atients with previous extensive anterior myocardial infarction from total left anterior descending artery (LAD) cclusion underwent exercise testing with equilibrium adionuclide ventriculography. Fifteen patients (SVD) had solated occlusion and 11 patients (MVD) had one or more dditional ≥70% stenosed coronary arteries.

The mean maximum heart rates in SVD (148±5) and MVD 146±5) patients were similar. Seven MVD patients but no VD patients developed angina and/or ischaemic ST changes ith exercise. In SVD patients, ejection fraction (EF) id not change from rest (0.32±0.03) to peak exercise 0.30±0.03) because there was a similar increase in end ystolic volume (ESV; 19%±4%) and end diastolic volume EDV; 16%±4%). In MVD patients EF decreased from 0.32± .03 to 0.23±0.02 ($p<0.01$) because of a disproportionate ncrease in ESV (45%±13%) compared to EDV (27%±7%).

After extensive anterior myocardial infarction resting EF is a poor index of exercise capacity. The increase n cardiac output during exercise in patients with SVD nd previous anterior infarction is heart rate dependent ecause stroke volume does not change. In patients with IVD the cardiac output response to exercise is attenuated ecause end systolic volume increases and stroke volume ecreases. This response to stress after myocardial nfarction may be important for early identification of atients with a poor prognosis due to residual ischaemic yocardium.

ASYMPTOMATIC LEFT MAIN CORONARY ARTERY DISEASE
Fayaz A. Shawl, MD; MRCP; Mitchell L. Mutter, MD; Dennis J. Donohue, MD; Robert D. Siama, MD; Rus Zajtchuk MD; James E. Davia, MD; Walter Reed Army Medical Center, Washington, D.C.

The prognosis, detection, and natural history of severe, asymptomatic coronary astroy disease remain difficult clinical problems. Epidemiologic studies of unexpected death and post-mortem studies of silent myocardial infarction suggest that this entity may be more common. We reviewed 89 consecutive patients with significant left main coronary artery disease (LMD), defined as 50% or greater reduction of luminal diameter. Of this group 10 pts (11%) were asymptomatic (ALMD) and 79 pts (88%) were symptomatic. All 10 ALMD pts were males with a mean age of 53 years (range 40-65). Treadmill test (TMT) were performed in this group for the following reasons: EKG abnormalities, 6; pre-jogging evaluation 2; risk factor evaluation 2. The TMT showed 2mm or greater ST depression in 7/10 (70%) and 1-2mm in 3/10 (30%). Similar TMT results were obtained in the SLMD group, although 2 patients had negative responses. The degree of stenosis of the left main coronary artery and the frequency of 3-vessel disease was similar in both groups. LV functions in ALMD group was excellent as manifested by a normal ejection fraction and normal wall motion in all 10 pts and a normal left ventricular end-diastolic pressure (LVEDP) in 70%, whereas in SLMD group 63% had an abnormal ejection fraction, 62% had wall motion abnormalities and 57% had a normal LVED.
In conclusion 1) 11% of LMD patients were asymptomatic 2) No significant difference was found in the TMT response and anatomy in the ALMD and SLMD group and 3) the ALMD group had much better LV functions when compared to the SLMD group.

ROGNOSTIC SIGNIFICANCE OF LEFT MAIN EQUIVALENT STENOSIS
lartin J. Conley, M.D., Victor S. Behar, M.D., F.A.C.C., rank E. Harrell, Ph.D., Robert M. Califf, M.D., Robert . Rosati, M.D., Duke University Medical Center, Durham, lorth Carolina

Concomitant ≥75% stenosis of the left circumflex proximal o the first marginal and ≥75% stenosis of the left nterior descending proximal to the first septal perforator and the first anterolateral have been considered o carry risk equivalent to ≥75% left main stenosis. The urpose of this study was to determine the prognostic ignificance of left main equivalent (LME) stenosis. mong 1527 consecutive medically treated patients with ignificant (≥75%) coronary artery disease, long-term urvival was significantly ($p=0.001$) lower for 90 patients ith ≥75% left main (LM) stenosis than for 57 patients ith LME stenosis:

	6 mo.	1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.
LM	73%	66%	52%	42%	40%	36%
LME	84%	76%	72%	63%	61%	54%

ultivariable analysis using a series of baseline haracteristics which we have previously demonstrated to e independent predictors of survival (including left entricular ejection fraction and number of vessels with ignificant stenoses) confirmed the prognostic importance f LM stenosis ($p<0.001$) but failed to demonstrate rognostic importance for LME stenosis ($p>0.20$). LME tenosis, therefore, does not carry risk equivalent to LM tenosis.

TOTAL OCCLUSION OF THE LEFT MAIN CORONARY ARTERY: THE CASS EXPERIENCE.
Samuel H. Zimmern, M.D., William J. Rogers, M.D., F.A.C.C., Peter R. Bream, M.D., Bernard R. Chaitman, M.D., F.A.C.C., Martial G. Bourassa, M.D., F.A.C.C., Kathryn A. Davis, Ph.D., Denis H. Tyras, M.D., Robert Berger, M.D., F.A.C.C., Lloyd Fisher, Ph.D., F.A.C.C., Melvin P. Judkins, M.D., F.A.C.C., Michael B. Mock, M.D., F.A.C.C., and Thomas Killip, M.D., F.A.C.C. University of Alabama in Birmingham, Birmingham, Alabama.

Total occlusion of the left main coronary artery (100%-LMCA) was confirmed on review of cineangiograms in 12 (0.05%) of the 23,349 patients (pts) entered into the Coronary Artery Surgery Study (CASS) prior to coronary surgery. These 12 pts are the largest reported group with 100%-LMCA.

Mean age at presentation was 58.9 yrs (range 44-80). Ten pts were male. Eleven pts had angina pectoris (AP) as their presenting complaint; 10 had Class III or IV AP; 4 had unstable AP. Chest pain first had been noted a mean of 231 wks (range 3 wks-14 yrs) prior to entry; the presenting level of symptoms had existed a mean of 24.4 wks (2-104 wks). Six pts had a myocardial infarction and 2 had congestive failure prior to entry. One pt presented with only a changed ECG.

During follow up 4 pts died a mean of 43.5 days after entry; 8 were living a mean of 37.6 mos after entry. The mean age on entry in the group that died was 70 yrs and in the surviving group 53.2 yrs. Seven pts had coronary artery bypass graft surgery (CABG); of these, 6 (86%) were surviving a mean 41.7 mos after CABG; 4 of these pts were free of angina. Five pts did not have CABG; of these, 2 (40%) were surviving a mean of 24 mos after entry, and 1 was free of angina.

Conclusions: 1.) Total occlusion of the left main coronary artery is a rare lesion. 2.) Most pts present with severe angina of prolonged duration. 3.) Advanced age worsens long-term prognosis. 4.) Prolonged survival and improvement of symptoms may occur following CABG. 5.) Long-term survival without angina is possible even without CABG.

MONDAY, MARCH 16, 1981
PM
LEFT VENTRICULAR DYSFUNCTION FROM HYPERTROPHIC CARDIOMYOPATHY AND VALVULAR CAUSES
4:00-5:30

LONG-TERM EFFECTS OF VERAPAMIL ON LEFT VENTRICULAR DIASTOLIC FILLING IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Robert O.Bonow, M.D., Douglas R.Rosing, MD, Stephen L. Bacharach, PhD, Michael V.Green, MS, Lewis C.Lipson, MD, John R.Condit, BS, Kenneth M.Kent, MD,FACC, and Stephen E.Epstein, MD, FACC, NHLBI, Bethesda, Maryland

Oral verapamil (V) therapy improves exercise tolerance and reduces symptoms in many pts with hypertrophic cardiomyopathy (HCM). We previously showed, using high resolution radionuclide LV time-activity curves, that abnormalities in LV diastolic filling (reduced peak LV filling rate (PFR) or prolonged time to PFR) are improved in pts with HCM after 1 week of V therapy, while systolic function is unaltered. To determine whether these improvements persist during long-term V therapy, we restudied 17 pts after 1 year of therapy before and after withdrawal from V. We found the following changes (mean ±SD) in PFR, measured in end-diastolic volumes (EDV)/sec, and in time to PFR:

	PFR (EDV/sec)	P		Time to PFR (msec)	P	
Control	3.2±1.1	<.001		170±43	<.01	
V-1 week	4.1±1.3		NS	157±31		<.05
V-1 year	3.5±1.3	<.005		187±39	<.001	
Control-1yr	3.0±1.0	<.005		204±46	<.05	

LV systolic function (ejection fraction, peak ejection rate and ejection time) did not change after 1 week of V, after 1 year of V, or after withdrawal from V at 1 year. Thus, 1) chronic V therapy does not alter LV systolic function in pts with HCM, and 2) initial improvements in LV diastolic filling induced by V decline over the course of 1 year, although V continues to exert persistent reversible beneficial effects in diastolic filling.

HYPERTROPHIC CARDIOMYOPATHY: MEASUREMENT OF CATION UPTAKE

William J.McKenna, M.D., Roger M.Allan, MB,FRACP, Peter Horlock, LRIC, J.C.Clark, BSc, P.M.Grant, H.A. O'Brien, Celia M.Oakley, MD,FACC, John F.Goodwin, MD,FACC, Andrew P.Selwyn, MB, MRCP. Royal Postgraduate Medical School, MRC Cyclotron Unit, Hammersmith Hospital,London, UK and Los Alamos Scientific Laboratory, Los Alamos, New Mexico.

The metabolic characterisation of myocardial tissue in hypertrophic cardiomyopathy (HCM) is under investigation. Positron tomography permits the quantitative assessment of the regional cation uptake by myocardium. Six patients with HCM and asymmetric septal hypertrophy and 6 normal subjects were studied. Transmission scans at 4 myocardial levels, 1.5 cm apart, were performed to later correct for tissue attenuation. Emission tomograms, at these 4 levels, were performed during the steady state intravenous infusion of Rubidium 82 (82Rb) ($t_{1/2}$= 78 sec) and 30 sec after cessation of the infusion. Computer reconstructed images were recorded on matrix printouts and the myocardium delineated. The arterial concentration of 82Rb was determined from the steady state imaga data and extraction x flow was calculated. Values were obtained for regions within the interventricular septum and the left ventricular posterior wall. Partial volume effects were corrected using M mode echocardiographic measurements. The ratio of left ventricular posterior wall to septal counts was calculated for all studies. The mean ratio for patients with HCM, 1.16 ± 0.054 (SEM), was significantly different from the mean ratio for the normals 1.02 ± 0.068 (P<0.005). These results in patients with HCM and asymmetric hypertrophy show regional differences in cation uptake which are not seen in normal subjects. These results suggest an abnormality of cation extraction and/or tissue perfusion in hypertrophic cardiomyopathy. (82 Strontium courtesy of Los Alamos).

MYOCYTE DISARRAY DEVELOPS IN PAPILLARY MUSCLES RELEASED FROM NORMAL TENSION AFTER MITRAL VALVE REPLACEMENT

John S. Pirolo, BS, Grover M. Hutchins, MD, G. William Moore, MD, PhD, and Myron L. Weisfeldt, MD, FACC, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Papillary muscles have an orderly array of myocytes aligned parallel to lines of tension. We examined the histologic effects of abrupt removal of tension on myocytes in left ventricular papillary muscles of 82 patients with mitral valve replacements, of whom 16 died at operation, 46 within one month, and 20 from 31 days to 15 years post-operation. Focal contraction band necrosis in 54 (66%) cases and fibrosis in 69 (84%) cases occurred in all three survival groups. Zonal lesions, sarcoplasmic condensations adjacent to intercalated discs, in 49 (60%) cases were prominent early, and correlated negatively with survival time (p<0.005). Myocyte disarray in 25 (30%) cases developed progressively with longer survival time (p<0.001) to become a pattern of an interconnecting, random network of myocytes. Myocyte atrophy in 16 (20%) cases correlated with degree of acquired disarray (p<0.001). Multivariate regression analysis with these five histologic features as predictors of survival time showed significant prediction by myocyte disarray only (p<0.001). Since the post-surgical papillary muscles studied approach an idealized isotonic contraction, it appears that myocyte disarray may be acquired over time in such a physical state. The study supports the concept that myocyte orientation arises as a direct consequence of force distribution in the myocardium.

ABNORMAL MITRAL ANNULAR CONTRACTION IN CARDIOMYOPATHIES AND CORRELATION WITH LEFT VENTRICULAR FUNCTION.

John A. Ormiston, MB ChB, FRACP, Pravin M. Shah, MD, FACC, Chuwa Tei, MD, Harvey Hecht, MD, FACC. University of California, and Wadsworth VA Medical Center, Los Angeles, California.

Wide angle phased array two-dimensional echocardiography was used to examine mitral annular areas and changes during the cardiac cycle in 12 normals (Nl), 8 patients (pts) with dilated cardiomyopathy (DCM) and 9 with hypertrophic cardiomyopathy (HCM). The echocardiographic transducer was placed over the palpable left ventricular apex and multiple planes around the circumference of the annulus recorded by sequential 30° rotations of the transducer. Annular diameters from each plane were used to reconstruct the annular circumference for selected times during the cardiac cycle. Enclosed areas were planimetered. Annular area reduction was calculated by expressing as a percentage the ratio (maximum diastolic area minus minimum systolic area) ÷ (maximum diastolic area). Radionuclide ejection fraction (EF) was obtained by equilibrium blood pool imaging after in vivo red blood cell labelling with technetium^{99m} in 7 DCM pts, 5 HCM pts and 1 Nl. Systolic annular area reduction was 27±3% (mean±SD) in Nls 10±6% in DCM and 39±3% in HCM. The differences between Nl and DCM as well as Nl and HCM were significant (p<0.001). There was a high correlation between systolic annular area reduction and radionuclide EF (r=0.935, SEE=6).

In conclusion 1) systolic annular area reduction is decreased in DCM and increased in HCM, 2) a high correlation between annular area reduction and EF suggests a direct relationship with pump function.

LEFT VENTRICULAR DYSFUNCTION IN PATIENTS WITH MITRAL REGURGITATION

Lewis C. Lipson, MD, Kenneth M. Kent, MD, FACC, Robert O. Bonow, MD, Douglas R.Rosing, MD, Charles L.McIntosh, MD, Michael Jones, MD, Andrew G.Morrow, MD, Stephen E. Epstein, MD, FACC, NHLBI, NIH, Bethesda, Md.

To determine optimum time for valve replacement in pts with mitral regurgitation (MR), we prospectively studied echo, radionuclide (RN) angiography, and hemodynamics in 21 pts with MR and severe symptoms who subsequently underwent operation (op). These studies were compared to those obtained in 17 mildly symptomatic pts who were followed (nonop). Pre-op, there were no significant differences between op and nonop pts in echo LV diastolic dimension (64±11 vs. 66±11), RN ejection fraction at rest (EFrest) (53±9 vs.51±8) or during exercise (EFex)(57±11 vs.56±12). At rest op pts had higher RA pressure (11±4 vs.5±3, p<.001) and PAW pressures (26±8 vs. 14±5, p<.001), but similar CI (2.3+.7 vs 2.5±.7, NS) compared to nonop pts. During supine exercise, despite similar elevations of PAW pressure (38±9 op vs. 31±14 nonop, NS) op pts had a lower CI (3.4±1.2 vs. 5.5±1.8, p<.005) than nonop pts. Postop, despite improvement in RA (11±4 to 8±4, n=13, p<.05) and PAW pressures (24±8 to 18±6, n=13, p<.05), CI was unchanged (2.2±.6 preop vs. 2.6±.8 postop, n=13, p<.05). Postop there was a marked reduction in EFrest (38±10 vs. 51±10 preop, n=13, p<.05) and EFex (41±12 vs.56±12 preop, n=12, p<.01); 10/13 pts had subnormal (<45%) EFrest and 11/12 pts had subnormal (<54%) EFex. Postop EFex was inversely related to preop LVDD and PAW at rest. We conclude that in pts with MR (1) LV dilatation occurs before severe symptoms develop and (2) by the time pts become severely symptomatic, irreversible LV dysfunction has occurred despite normal preop RN EF, a result of LV decompression into a low pressure LA.

LEFT VENTRICULAR EJECTION RATE DURING THE FIRST THIRD OF SYSTOLE IN PATIENTS WITH AORTIC INSUFFICIENCY

Lynne L. Johnson, MD, Mitchell Marshall, BS, Yvonne E. Johnson, MD, Paul J. Cannon, MD, FACC, Columbia U New York

In previous studies the rate of LV volume change during the first 1/3 of systole was shown to be a more sensitive index of cardiac performance than ejection fraction (EF) in coronary disease. To test the hypothesis that a non-invasive index of the ejection rate in early systole can also identify subtle abnormalities of LV performance in aortic insufficiency (AI) the rate of change of LV counts during the first 1/3 of systole was measured by first pass radionuclide angiography in 26 patients. By weighted least squares a monoexponential equation was fit to the LV counts obtained at 0.025 second intervals during the first 1/3 of systole; the slope was divided by the average counts in the first 1/3 to give a rate constant (RC) proportional to LV volume change during early systole.

The patients were divided into two groups based upon the response of EF to exercise (ΔEF). In group I resting EF was .59±.08 and increased .10±.04 during exercise; in group II resting EF was not different (.58±.08) but fell during exercise (-.08±.06) ($p<.001$). The RC obtained at rest was 15.7±4.0 in group I and was significantly lower in group II, 9.5±3.0 ($p<.001$). Using an RC of 12.0 as a cut-off and applying the Fisher exact test, separation of the groups was excellent ($p<.001$) with only one group I patient with RC<12.0 and 2 in group II with RC>12.0. When RC was plotted vs EF for the 26 patients, there was a significant direct relationship, $r = 0.76$ ($p<.01$) but with wide confidence limits.

The data indicate that a non-invasive index of the rate of LV volume change during the first 1/3 of systole can identify abnormal LV reserve in patients with AI and normal EF at rest.

MONDAY, MARCH 16, 1981
PM
DIASTOLIC MECHANICS OF THE HEART AND PERICARDIUM
4:00-5:30

SYSTOLIC LOAD DEPENDENCY OF LEFT VENTRICULAR RELAXATION IS INFLUENCED BY BETA ADRENERGIC TONE AND ABNORMAL SYNCHRONY.

Alvin S. Blaustein MD, William H. Gaasch MD FACC, John D. Carroll MD, Dan Adam PhD and Herbert J. Levine MD FACC. Tufts-New England Medical Center Hospital and Harvard-Beth Israel Hospital, Boston, MA.

The relation between LV relaxation velocity and systolic load (pressure) was examined in 18 open chest anesthetized (chloralose-morphine) dogs (constant heart rate,2 Hz). LV pressure (P) was measured with a micromanometer and the time constant (T,ms) of LV isovolumic P decline was taken as an index of LV relaxation velocity. A progressive increase in LV systolic P was produced by abrupt diastolic cross clamp of the descending thoracic aorta; the clamp was maintained for 3 beats and then released,thus generating 4 end systolic (ES) P-T coordinates. Over a wide range of ESP (95-200 mmHg.) the ESP-T relation was linear (least squares best fit, r=+0.98). By definition,the slope (k) of this relation reflects the load dependency of T.

Values of T and k were determined before (control, C) and after each of three interventions: isoproterenol (Iso), propranolol (Pro), and LV asynchrony (Asyn). Asynchrony was produced by RV free wall pacing; all other studies were performed with RA pacing. Data below are mean±SE; *=$p<0.05$: T_{120}=T at a common ESP of 120 mmHg.

	C	Iso	C	Pro	C	Asyn
T_{120}	26±2	22±3*	20±3	27±4*	24±2	30±3*
k	.16±.01	.09±.01*	.11±.01	.29±.04*	.09±.02	.25±.04*

Thus, the time constant of LV pressure decline is load dependent; this load dependency is decreased by isoproterenol and increased by propanolol and asynchrony. Changes in sympathetic tone presumably influence relaxation through subcellular or biochemical processes, while asynchrony likely influences the load dependency of T by changing the distribution of load over functioning myofibrils and/or by causing temporal dispersion of relaxation.

MECHANISMS OF LOAD INDEPENDENCE OF RELAXATION DURING HYPOXIA IN MAMMALIAN CARDIAC MUSCLE

Stanislas U. Sys; Philippe R. Housmans, M.D.; Eric R. Van Ocken, Ph.D.; Dirk L. Brutsaert, M.D., Ph.D. Dept.of Physiology, University of Antwerp, Antwerp, Belgium.

In mammalian cardiac muscle relaxation, which is very sensitive to the prevailing load, was recently shown to become largely load-independent during hypoxia. This effect was ascribed to a delayed removal of the activating myoplasmic calcium.

To further elucidate the underlying mechanisms of this effect of hypoxia, relaxation was now studied in 20 cat papillary muscles (29° C; 12/min; $(Ca^{2+})_o$ 2.5 mM) at low $(Ca^{2+})_o$ (1.0, 0.5, 0.375 mM) or after verapamil (10^{-6} M). Load dependence of relaxation was quantified by comparing force and time coordinates at the onset of the isometric relaxation phase in several afterloaded isotonic twitch contractions with the relaxation of the isometric control contraction. Low $(Ca^{2+})_o$, verapamil and hypoxia reversed relaxation from load-dependent into load-independent. Although low $(Ca^{2+})_o$ and verapamil had a more marked negative inotropic effect on the contraction phase than hypoxia, the reversal of relaxation from load-dependent into load-independent was significantly more pronounced with hypoxia. Even when hypoxia was superimposed on low $(Ca^{2+})_o$ or verapamil, the same marked degree of load dependence was attained as during hypoxia alone. The mechanisms by which low $(Ca^{2+})_o$ and verapamil result in load-independence of relaxation, probably by slowing down the removal of activating myoplasmic calcium, are still not fully understood. However, hypoxia exerts an additional disturbing effect on relaxation through other, probably energetically-linked aspects, e.g. the ATP-dependent detachment of the actinomyosin interactions.

THE EFFECT OF VERAPAMIL ON THE DIASTOLIC MECHANICS OF THE LEFT VENTRICLE

Peter Van Trigt, M.D.; Craig O. Olsen, M.D.; Gary L. Pellom, M.S.; Robert B. Peyton, M.D.; Robert N. Jones, M.D.; J. Scott Rankin, M.D.; Andrew S. Wechsler, M.D., Duke University, Durham, North Carolina

Verapamil (V), an antagonist of ionized calcium (Ca++) influx, has been shown to depress LV systolic performance; however, little is known of its effect on diastolic function. The effect of V on the diastolic mechanical properties of the LV was studied in 7 conscious dogs previously instrumented with epicardial ultrasonic dimension transducers to measure LV minor axis diameter. LV transmural pressure was measured with micromanometers. LV pressure and dimension data were recorded and computer analyzed during transient vena caval occlusions in the control state and following a 20 minute intravenous infusion of V (.01 mg/kg/min) which decreased peak LV pressure 131.0±2.6 to 117.3±2.2 mm Hg ($p<.01$), peak dp/dt 2043±260 to 1834±284 mm Hg/sec, and peak dL/dt -51.95±2.2 to -48.3±2.1 mm/sec ($p<.05$). Static diastolic diameters were normalized according to Lagrangian strain (ε), and the pressure strain data were fitted to $P=\alpha(e^{\beta\varepsilon}-1)$, where α and β are nonlinear elastic coefficients of the myocardium. Strain data (mean ± SEM) at specific end diastolic pressures (5,10,15,20 mm Hg) were compared during control and after V (*=$p<.05$).

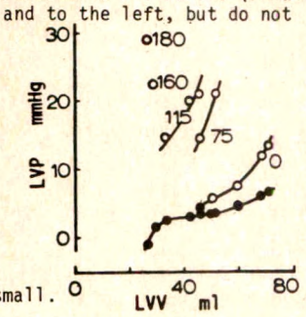
	$\varepsilon 5$	$\varepsilon 10$	$\varepsilon 15$	$\varepsilon 20$
Control	.078±.003	.117±.005	.146±.005	.168±.006
Verapamil	*.088±.004	*.132±.005	*.161±.006	*.188±.008

In addition, myocardial elastic constants were changed by V for each dog. Thus, V caused a significant shift to the right of the diastolic pressure-strain relationship, indicating an increase in LV diastolic compliance. These data suggest that by decreasing Ca++ influx into the region of the myofibrils, V impairs systolic function and alters the diastolic material properties of the myocardium.

SHIFTS IN LEFT AND RIGHT VENTRICULAR DIASTOLIC PRESSURE-VOLUME CURVES DUE TO PERICARDIAL EFFUSION AND TAMPONADE

John V. Tyberg, MD, FACC; Michael Junemann, MD; Helge Refsum, MD; Erik Carlsson, MD; Martin J. Lipton, MD, FACC CVRI, University of California, San Francisco, CA.

We studied the effects of pericardial effusion and tamponade on LV and RV pressure-volume (P-V) relations using computed tomography with contrast medium enhancement to measure pericardial and intracardiac volumes of 16 anesthetized closed chest dogs. The areas of the computed tomographic cross-sections were measured at 1 cm intervals from apex to base. We used flat saline-containing balloons to measure pericardial and pleural P. Pericardial effusion and tamponade, produced by infusing warmed dilute contrast medium, increased pericardial P by dilating the pericardium along its P-V curve. In the experiment shown open symbols represent LV P relative to atmospheric P; solid symbols represent transmural LV P (LV P - pericardial P). The numbers indicate the volume (ml) of pericardial fluid. Pericardial effusion and tamponade shift LV and RV diastolic P-V curves (relative to atmospheric P) upward and to the left, but do not affect the LV and RV diastolic transmural P-V curves. In pericardial effusion and tamponade elevated LV and RV diastolic P indicate elevated pericardial P; however, transmural ventricular diastolic P may approach zero and ventricular diastolic volumes may become very small.



QUANTIFICATION OF PERICARDIAL INFLUENCES ON DIASTOLIC FILLING OF THE LEFT VENTRICLE.

George S. Tyson, Jr., M.D., Craig O. Olsen, M.D., James W. Davis, M.S., J. Scott Rankin, M.D., David C. Sabiston, Jr., M.D., Duke University Medical Center, Durham, N.C.

In eight conscious, chronically instrumented dogs left ventricular (P_{LV}), pericardial (P_{PC}), and pleural (P_{PL}) pressures were simultaneously measured with matched micromanometers and minor axis left ventricular (LV) diameter was measured with ultrasonic transducers. During implantation, the pericardium was incised transversely at the base of the heart and then was precisely reapproximated so that its characteristics were minimally disturbed. Data were recorded during control conditions, during vena caval occlusions, and after volume loading such that LV diastolic transmural pressure (P_{LV}-P_{PL}) was varied from 0-25 mmHg. At normal diastolic volumes, the absolute P_{PC} varied with the P_{PL} through the respiratory cycle, but the transpericardial pressure (P_{PC}-P_{PL}) remained constant at approximately 0 mmHg. At maximum diastolic volumes obtained after volume loading, transpericardial pressure averaged 4.2 mmHg and accounted for less than 20% of LV transmural pressure. The exponential diastolic LV transmural pressure-dimension relationship remained essentially constant whether P_{PC} or P_{PL} was used as the external pressure; the differences observed were minimal and occurred at higher diastolic volumes. Thus, when measurements are made precisely, transpericardial pressure remains low over the entire physiologic range of measurements. Furthermore, the pericardium does not significantly affect diastolic filling of the LV at normal end diastolic volumes, and even at maximum volumes its influence is minimal.

ALTERATIONS IN LEFT VENTRICULAR GEOMETRY DURING INSPIRATION IN THE CONSCIOUS DOG.

Craig O. Olsen, M.D., Peter Van Trigt, III, M.D., Gary Pellom, M.S., Andrew S. Wechsler, M.D., J. Scott Rankin, M.D., Duke University Medical Center, Durham, N.C.

The mechanisms of respiratory variations in left ventricular (LV) function were investigated in eight conscious dogs instrumented with ultrasonic transducers to measure LV anterior-posterior (D_{AP}) and septal-free wall (D_{SF}) diameters. LV, right ventricular (RV) and pleural (Pl) pressures (P) were measured with matched micromanometers. Data were recorded during spontaneous deep inspirations (Mueller maneuver) and analyzed by digital techniques. During inspiration PlP decreased by -11.5±1.7 mmHg, LV transmural pressure (TMP=LVP-PlP) and D_{AP} increased, while LV transeptal pressure (TSP=LVP-RVP) and D_{SF} decreased. Data are presented (mean±SEM) for spontaneous deep inspirations at end expiration (EE) and end inspiration (EI):

	mmHg			mm	
	PlP	TMP	TSP	D_{AP}	D_{SF}
EE	-2.3±0.2	10.6±1.3	5.4±0.8	68.1±2.0	60.3±1.9
EI	-13.8±1.8	14.5±2.2	3.6±1.4	69.6±2.1	59.7±1.8
P(t)	<.01	<.05	<.05	<.01	<.05

Thus, during the respiratory cycle, D_{AP} varied directly with the TMP gradient while D_{SF} changed with the TSP gradient. With inspiration LV minor axis geometry deformed eccentrically possibly secondary to increased venous return to the RV which decreased the TSP gradient. Therefore, impaired filling of LV due to septal shifting may be one mechanism producing decreased LV stroke volume during spontaneous inspiration.

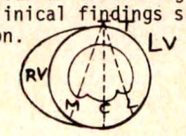
MONDAY, MARCH 16, 1981
PM
ECHOCARDIOGRAPHY: VALVULAR DISEASE
4:00-5:30

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC IDENTIFICATION OF PROLAPSE OF INDIVIDUAL SCALLOPS OF POSTERIOR MITRAL LEAFLET

Bapineedu Gondi, MD; Navin C. Nanda, MD, FACC; James Hodsden, MD; University of Rochester Medical Center; Rochester, New York

The posterior mitral leaflet (PML) usually has 3 scallops and 1 or more of these scallops may be affected by myxomatous changes and prolapse into LA during systole. Echocardiographic identification of individual scallops has not been described previously. In 12 patients (pt) isolated PML prolapse was identified by real time two-dimensional echocardiography (ATL 90° sector scanner) in standard parasternal and/or apical four-chamber view. The mitral valve (MV) was then scanned from base to tip in short axis plane to view indentations which divided the posterior leaflet into scallops. M-mode tracings were obtained from the short axis views of the MV by passing a cursor through the scallop areas and were evaluated for systolic MV prolapse. In our experience, PML prolapse occurs in a supero-posterior direction and this technique detects the posterior component. Systolic prolapse into LA involved all scallops in 6 pt (50%), central and medial scallops in 5 pt (42%) and central scallop alone in 1 pt (8%). Auscultatory evidence for mitral regurgitation was more commonly seen in pt with 3-scallop prolapse (5/6 pt) than in pt with 2-scallop (2/5 pt). One pt with 3-scallop prolapse and another with 2-scallop prolapse had frequent ventricular premature beats. Echocardiographic identification of prolapse of individual posterior leaflet scallops may enhance our understanding of the syndrome and may correlate with clinical findings such as the degree of mitral regurgitation.

M: Medial
C: Central
L: Lateral



T: Transducer
----: M-mode cursor

ECHOCARDIOGRAPHIC EVALUATION OF TRICUSPID ANNULUS SIZE AND FUNCTION IN NORMAL AND IN TRICUSPID REGURGITATION.

Chuwa Tei, MD, Pravin M. Shah, MD, FACC, John A. Ormiston, MD, Maylene Wong, MD. University of California, Los Angeles, and Wadsworth VA Medical Center, Los Angeles, CA.

Using wide angle phased array two-dimensional echocardiography, tricuspid leaflets and annular attachments were recorded by placing the transducer in an intermediate position between the left sternal edge and the apex. The transducer was then rotated and recordings obtained at 30° rotational intervals around the circumference of the tricuspid annulus. At each rotational interval, the largest annular diameter observed, at end of the P wave on EKG (max. diameter); and the smallest at midsystole (min diameter) were measured, and max and min annulus areas were reconstructed. Annular areas were planimetered and annular circumferences measured using a wheel. The annular area index (cm^2/m^2) and the annular circumference index (cm/m^2) were examined in 11 patients with tricuspid regurgitation (TR) secondary to long standing pulmonary hypertension or dilated cardiomyopathy; and 10 normal subjects (N). Annular area and circumference index in TR were significantly larger than N. However, their systolic reductions were signigicantly smaller than N.

	Area Index (cm^2/m^2)			Circumference Index (cm/c^2)		
	max	min	reduction	max	min	reduction
N(n=10)	3.7±0.6	2.1±0.3	42±4%	4.9±0.4	3.8±0.3	23±4%
TR(n=11)	6.6±0.8	4.7±0.8	29±6%	6.8±0.6	5.8±0.7	15±4%
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

In summary, a new echocardiographic approach to quantitative evaluation of tricuspid annular size and function is described. Our preliminary findings confirm in man an association between dilatation of the annulus and development of secondary tricuspid regurgitation. This quantitative evaluation may be useful in planning for tricuspid annuloplasty in TR patients undergoing surgery.

THE EVALUATION OF LEFT VENTRICULAR FUNCTION AT REST AND DURING EXERCISE BY TRANSESOPHAGEAL ECHOCARDIOGRAPHY IN AORTIC INSUFFICIENCY

Peter Kremer, M.D., Peter Hanrath, M.D., Burkhard Langenstein, M.D. Masayuki Matsumoto, M.D.; FACC, Carsten Tams, M.D., Walter Bleifeld, M.D., FACC.
Department of Cardiology, University Hospital, Hamburg, W.-Germany

During dynamic exercise transthoracical echocardiography is only of limited value for the evaluation of left ventricular (LV) performance. Therefore we studied LV function during maximal dynamic exercise by supine bicycle ergometry in 8 normal subjects (N) and 12 patients (pts) with symptomatic aortic insufficiency (AI) with transesophageal M-mode echocardiography. With this transesophageal approach where a special transducer is incorporated at the tip of a commercially available gastroscope good continuous recordings of the LV-dimension not disturbed by respiration or thoracical excursion during E were obtained. Systolic blood pressure (BP) measured by cuff and the following echocardiographic indices were determined before (R) and during maximal E: Heart rate (HR), enddiastolic dimension (ED), fractional shortening (FS) and the maximal velocity of fiber shortening (VCF_{max}).

		HR (min^{-1})	BP (mmHg)	ED (mm)	FS (%)	VCF_{max} (sec^{-1})
N	R	85±19	132±14	51± 8	36± 7	2.4±0.4
	E	145±17**	171± 23**	49 ± 9	47± 8**	3.9±0.6**
AI	R	89± 21	152± 22	64±10	35± 6	2.5±0.6
	E	128 ± 24**	176± 27**	62±10	31± 8*	2.3±0.8

± S.D., R vs. E: *p < 0.01, **p < 0.001

Conclusions: In N and in pts with AI ED was not changed at R and during E. However despite a normal systolic performance at R in AI FS decreased during E unmasking impaired LV systolic function.

QUANTITATION OF AORTIC REGURGITATION WITH TWO-DIMENSIONAL DOPPLER ECHOCARDIOGRAPHY

William J. Bommer, MD, FACC; Randall Mapes, BS; Larry Miller, PhD; Dean T. Mason, MD, FACC; Anthony N. DeMaria, MD, FACC, University of California, Davis, California

Present pulse Doppler (PD) techniques are able to detect the presence but not the severity of aortic regurgitant flow (AR). Therefore we assembled a customized pulse Doppler system to obtain detailed blood flow maps of the left ventricular outflow tract (LVOT) and compared the results with aortography in 25 patients (pts) with suspected AR. The PD system consisted of a two-dimensional (2-D) echo duplex scanner, a modified Doppler detector, a real-time fast Fourier transform (FFT) monitor, and a FFT processor which yielded digital estimators of the spectral spread in Doppler frequency or blood velocity. PD samples for blood flow mapping were obtained by scanning the total area of the left ventricular outflow tract (anterior to the mitral valve (MV) and papillary muscles (PM)) at three levels on 2-D echo short axis (SA) images: Level 1 - just inferior to the aortic valve; Level 2 - at the middle of the MV leaflets; Level 3 - at the PM's. Results showed that disturbed Doppler flow (DDF) was best defined by the digital estimator--median absolute deviation >1000 Hz. DDF was often eccentrically located in the LVOT, however SA mapping of the level and extent of DDF allowed excellent correlation with angiography (0 → 4+); for 8 pts without AR--no DDF was seen at any level (8/8); for 2 pts with 1+ AR--only Level 1 DDF was seen (2/2); for 5 pts with 2+ AR--Level 1 and 2 DDF was seen (5/5); for 5 pts with 3+ AR--Levels 1, 2 and 3 showed DDF (5/5); and for 5 pts with 4+ AR--DDF was seen at Levels 1 and 2, and extended over 50% of the SA area of Level 3 (5/5). Thus PD mapping of the level and extent of DDF allows quantitation of aortic regurgitation and provides valuable noninvasive information in these patients.

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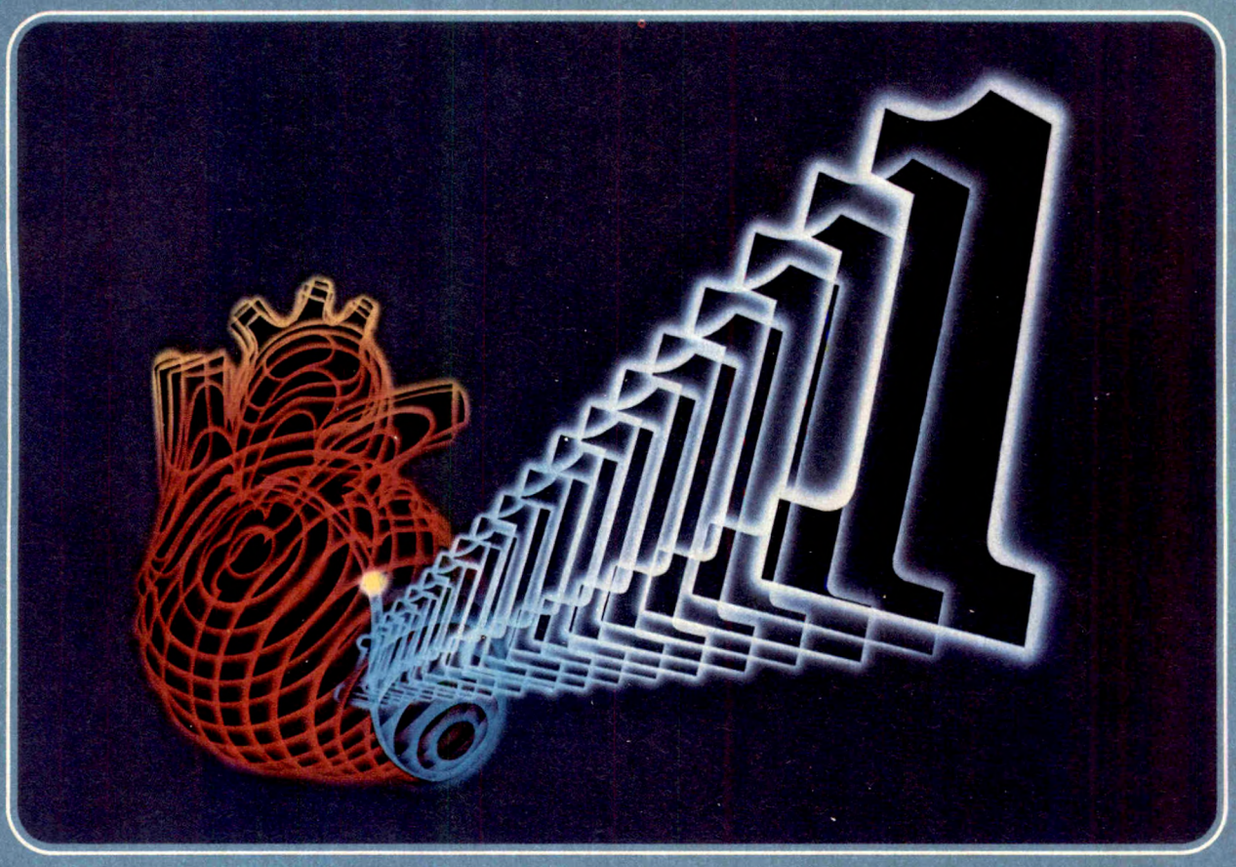

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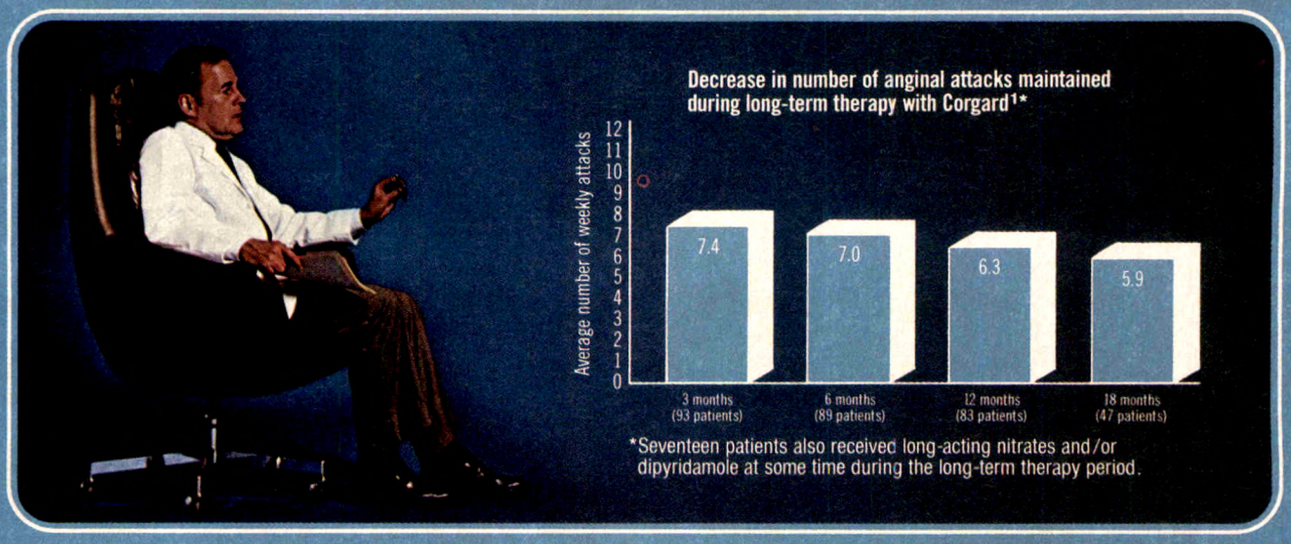

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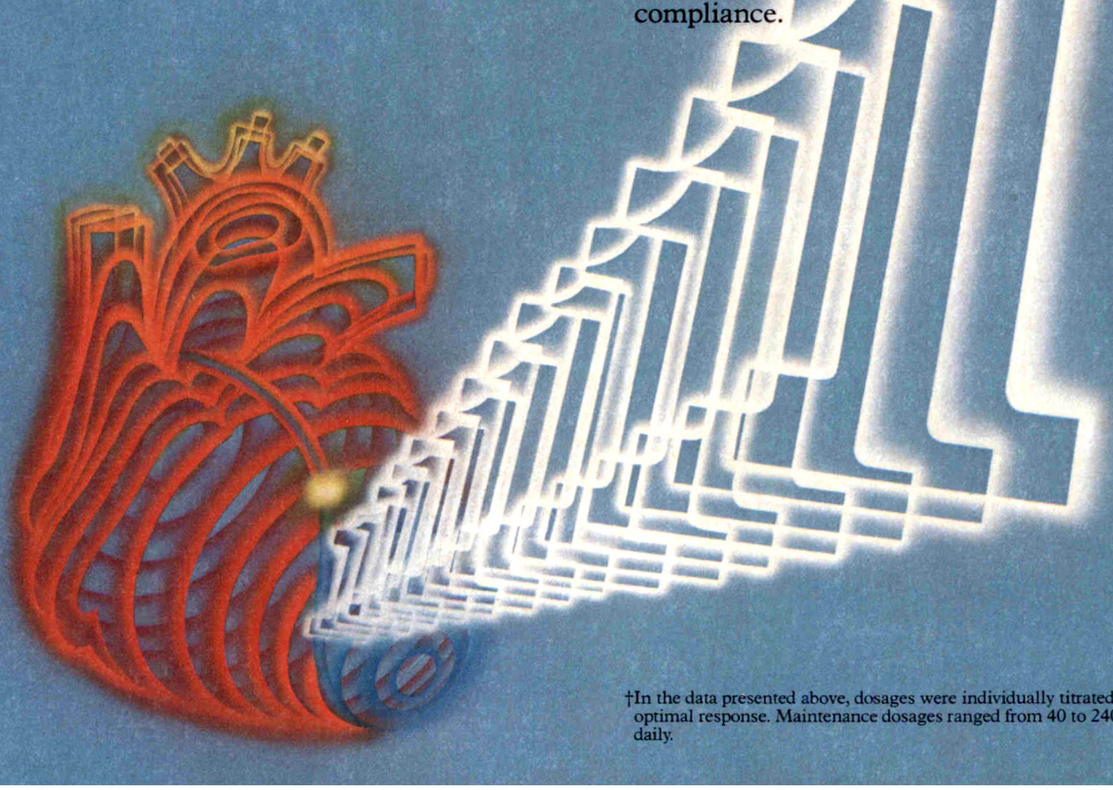
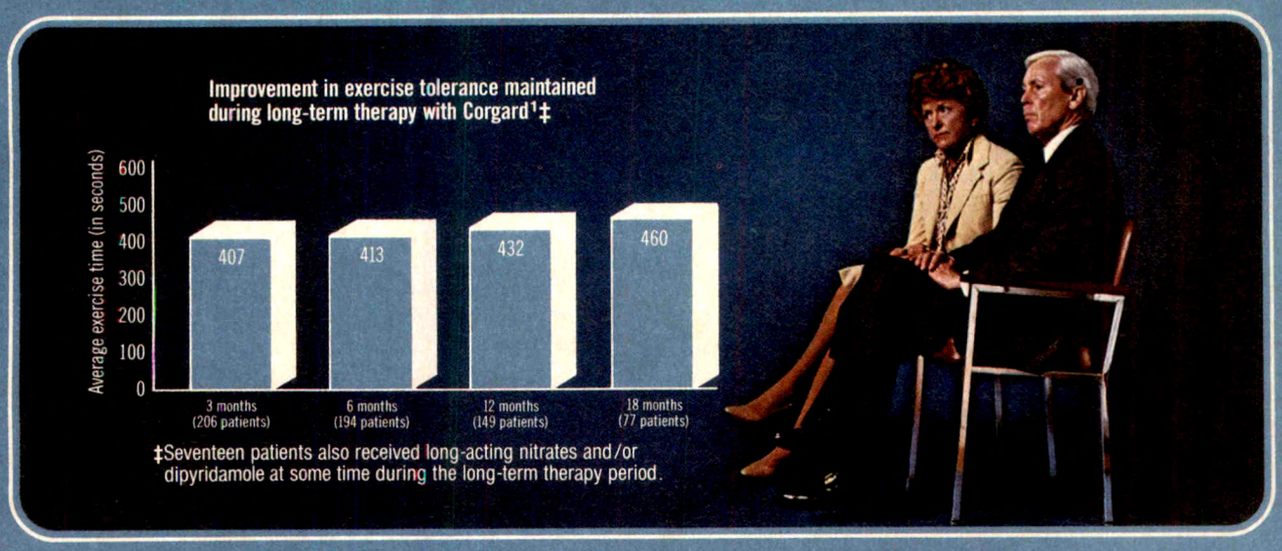


†In the data presented above, dosages were individually titrated to achieve optimal response. Maintenance dosages ranged from 40 to 240 mg Corgard daily.



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The common-sense beta-blocker for angina pectoris

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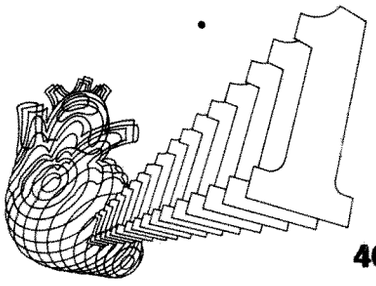
See next page for brief summary.

The only once-a-day beta-blocker for both angina pectoris and hypertension



CORGARD®
nadolol tablets
40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure— Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occur commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

Reference:

1. Data on file, Squibb Institute for Medical Research.

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Issued: January 1981

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EFFICACY OF AFTERLOAD REDUCTION IN AORTIC REGURGITATION: ASSESSMENT BY TWO-DIMENSIONAL ECHO

Martin St. John Sutton, MD, Nathaniel Reichek, MD, Ted Plappert, John A. Kastor, MD, FACC, Hospital of the University of Pennsylvania, Philadelphia, PA

To determine the effects of afterload reduction in the treatment of chronic aortic regurgitation(AR), we developed a method of assessing LV cavity size, wall thickness, and end-systolic wall stress using 2-dimensional echo and systolic cuff blood pressure(P). High-quality echoes of the LV short axis at mitral valve level and simultaneous systolic blood P were obtained in 12 patients with severe AR before and after 0.4 mg sublingual nitroglycerin. LV echograms were digitized to obtain cavity area(CA), and myocardial area(MA) and these results were corrected with a regression equation previously validated in vitro. End-systolic wall stress was calculated as 1.334 x P x CA/MA before and after nitroglycerin(NTG):

	P.(mm)	CA.(cm^2)	MA.(cm^2)	Wall Stress.(dynes/cm^2)
Before: (NTG)	130±20	15.5±9.0	32.2±6.5	79.0±25.8 X 10^3
After: (NTG)	121±17	14.6±8.6	32.1±6.5	69.0±24.8 X 10^3

Nitroglycerin significantly reduced P ($p<.01$), CA ($p<.005$), and end-systolic wall stress ($p<.02$) without any changed in MA or heart rate. In conclusion, we describe a new, reproducible and non-invasive method of assessing end-systolic wall stress, 2) demonstrate that in patients with AR nitroglycerin significantly reduced end-systolic LV size and wall stress, 3) since end-systolic wall stress is the critical factor limiting LV emptying, afterload reduction appears efficacious in the treatment of patients with chronic severe aortic regurgitation.

TWO DIMENSIONAL ECHOCARDIOGRAPHIC EVALUATION OF BRANCH PULMONARY ARTERY STENOSIS

Navin C. Nanda, MD, FACC; Mark S. Rosenzweig, MD; James E. Hodsden, MD; James A. Manning, MD; Shirley Santelli, Univ. of Rochester Medical Center, Rochester, New York

Real time two dimensional echocardiographic studies were performed in 6 patients (ages 5-25 years; 3 females, 3 males) with branch pulmonary artery stenosis proven by cardiac catheterization and angiography. The suprasternal approach was utilized using a commercially available transducer specially suited for this technique. The right pulmonary artery was visualized behind the aortic arch, and angling the transducer leftward brought the main and left pulmonary arteries into view. Discrete narrowing of the lumen at the origin of the left pulmonary artery was seen in one patient with an atrial septal defect, and at the origin of both right and left pulmonary arteries in another patient with tetrology of Fallot and atrial septal defect. Tubular narrowing of the right pulmonary artery was seen in one patient who had pulmonary valvotomy for pulmonary valve stenosis. The main pulmonary artery was large and prominently pulsatile. Tubular narrowing of the right pulmonary artery with post-stenotic dilatation of its distal portion was identified in one patient who had no other cardiac lesions. Diffuse narrowing of both the right and left pulmonary arteries was seen in one patient with mild pulmonary valve stenosis. A large left pulmonary artery with absent right pulmonary artery was identified in one patient with tricuspid atresia. All findings were confirmed at angio-cardiography. Abnormalities of the pulmonary artery branches could not be identified in any patient using the precordial or subcostal approach. Suprasternal two dimensional echocardiographic examination technique is useful in the evaluation of branch pulmonary artery stenosis and this represents a newer extension of the capability of this non-invasive method.

MONDAY, MARCH 16, 1981
PM
MYOCARDIAL METABOLISM
4:00-5:30

PHOSPHORYLATION OF CARDIAC SARCOPLASMIC RETICULUM (SR) BY A CALCIUM-ACTIVATED, PHOSPHOLIPID-DEPENDENT PROTEIN KINASE.

Constantinos J. Limas, M.D.; University of Minnesota School of Medicine; Minneapolis, Minnesota

A novel cyclic nucleotide-independent protein kinase (PK-C) has been isolated from rat heart cytosol. PK-C can phosphorylate cardiac SR (1.6±0.4 nmol/mg/10 min) in the presence of Ca^{2+} (10^{-7}-10^{-4} M $CaCl_2$) and phospholipids (2-20 µg/ml). Phosphatidylserine is most effective, followed by phosphatidylinositol and phosphatidyl-choline. Diacylglycerols containing unsaturated fatty acids (diolein,dilinolein,diarachidonin) stimulate PK-C by 50-75% by increasing its Ca^{2+} sensitivity. Saturated diacyl-glycerols, mono- and triacylglycerols, on the other hand, are ineffective. PK-C dependent phosphorylation of cardiac SR results in enhanced Ca^{2+} uptake (128±16 nmol Ca^{2+}) mg/min vs 82±9 nmol/mg/min in controls, $p<0.01$)and Ca^{2+} ATPase activity (63±7 nmol P_i/mg/min vs 46± 5 nmol/mg/min, $p<0.01$). PK-C may, therefore, be an important determinant of cardiac SR function by serving as a link between calcium fluxes and membrane glycerolipid metabolism. Stimulation of Ca^{2+} transport by cardiac SR is amplified by the increased Ca^{2+} sensitivity of PK-C mediated through unsaturated diacylglycerols.

METABOLISM OF ARRHYTHMOGENIC LYSOPHOSPHATIDES IN RABBIT MYOCARDIUM

Richard W. Gross, MD; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Missouri

Cardiac metabolism of lysophosphatidyl choline (LPC), implicated as a mediator of dysrhythmia induced by ischemia, has not been elucidated. To determine whether LPC transacylase acitivity, analogous to that in liver, is present in heart muscle, rabbit heart extracts were prepared by mincing; homogenization in 0.25 M sucrose (25% w/v), 1 mM DTT, 10 mM phosphate, pH 7.4; and centrifugation at 3,000, 8,000, 20,000 g for 10 min and 100,000 g for 1 hr. LPC-transacylase in the supernate was assayed in 800 µl of media containing 75 mM buffer, pH 5 to 9; 3 mM MgCl; 120 µM 1-^{14}C-LPC; and 600 µg protein incubated at 37° for 15 min; products extracted in 750 µl butanol and separated by HPLC; and radioactivity quantified. Transacylation, manifested as synthesis of 1,2-^{14}C-phosphatidylcholine (PC) occurred at a high rate (0.61 ± .07 (SE) nmols/mg protein/min (n = 6), displayed a sharp pH optimum at pH 7.0, and was linear with respect to incubation time and protein concentration. To identify the position of incorporated label, PC synthesized was isolated by HPLC and treated with snake venom phospholipase A_2. The ratio of labeled fatty acid to labeled LPC was 1.09 ± .11 (n = 4), demonstrating the initial presence of PC labeled in both the 1- and 2-positions. To detect other reactions such as direct acylation (LPC acyl transferase), cytosol was incubated under the same conditions with ^{14}C-palmitoyl CoA and unlabeled LPC. PC synthesis was < 10% of that seen with labeled LPC. Thus, rabbit heart cytosolic extracts exhibit considerable LPC transacylase activity (but not LPC acyl transferase) that does not require acyl CoA and that appears to contribute substantially to LPC metabolism.

FLOW-INDEPENDENT CHARACTERISTICS OF EXTERNALLY DETECTABLE CARDIAC KINETICS OF ^{11}C-PALMITATE

Steven R. Bergmann, PhD; Rene A. Lerch, MD; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Missouri

It has been suggested that flow-dependence of ^{11}C-palmitate kinetics precludes their use as an externally detectable measure of metabolism. To differentiate the independent effects of the two types of determinants, 15 isolated, paced, isovolumically beating rabbit hearts were perfused retrograde at constant flow at 37° with washed sheep erythrocytes in a modified Krebs-Henseleit buffer containing 0.4 mM albumin and equimolar palmitate. This preparation permits maintenance of flow within the physiological range. Myocardial time-acitivity curves, monitored in the coincidence mode for 20 min after aortic injection of 50 μCi of albumin-bound ^{11}C-palmitate, exhibited three distinct monoexponential phases, the first representing vascular transit. Deconvolution techniques indicated incorporation of 20.8 ± 1.9 (SE)% of tracer into a pool with a turnover rate constant (k) of 1.4 ± 0.6 x 10^{-3}min^{-1} ($t_{1/2}$ = 2.0 ± .2 min) and 15.0 ± 1.0% into a second pool with a k of .25 ± .05 x 10^{-3}min^{-1} ($t_{1/2}$ = 48.4 ± 10.6 min). Administration of 4.1 x 10^{-7}M epinephrine increased cardiac work and MVO_2 by 60%. Although flow was held constant, extraction of tracer into the first pool increased significantly ($p < .01$) to 89.2% without an increased turnover rate while turnover rate of the second pool increased markedly (k = 0.38 ± 0.04 x 10^{-3}min^{-1}, $t_{1/2}$ = 32 ± 3.2 min, $p < .01$ vs control). Thus, changes in fatty acid metabolism are readily detectable externally with ^{11}C-palmitate despite maintenance of constant flow, and should permit non-invasive quantitation of cardiac fatty acid utilization.

KINETICS OF C-11 LABELED PALMITATE IN ISCHEMIC MYOCARDIUM

H.R. Schön, MD; J.R. Robinson, PhD; H.R. Schelbert, MD; J.R. Barrio, PhD, UCLA School of Medicine, Los Angeles, CA

For future studies using positron emission computed tomography, single pass extraction fraction (E) and halftimes (T) of C-11 palmitate (CPA) in ischemic myocardium and their relationship to myocardial blood flow (MBF), oxygen consumption (MV) and myocardial CO_2 production were determined in 13 experiments in 7 open chest dogs. Following stenosis of the left anterior descending coronary artery and intracoronary injection of CPA, E and T of CPA were determined from the peak and slope of the myocardial time activity curve recorded with a scintillation probe for 60 minutes. The curve consisted of a vascular phase, an early rapid (R) and a slow phase (S). T of R increased with reduced MBF (T=13.46-0.11 MBF, r=0.74) and reduced MVO (T=13.77-0.74 MVO, r=0.83), while T of S was not influenced by MBF and MVO. Peak C-11 CO_2 production of ischemic myocardium, determined from MBF and the arteriovenous C-11 CO_2 difference, fell with decreased MBF by y=1503 exp (0.04 MBF), r=0.85. T of C-11 CO_2 production correlated with T of R (y=0.21+0.89x, r=0.98). The ratio of peak C-11 CO_2 production and peak CPA washout averaged 1.59±.14 and fell with decreased MBF (r=0.81). E averaged .60±0.09 and did not change significantly with altered MBF and MVO. E of R (ER) fell with decreased MBF (ER=1.77+0.16 MBF, r=0.70) and MVO (ER=12.33+1.22 MVO, r=.73), whereas E of S (ES) increased with decreased MBF (ES=57.70-2.34 MVO, r=0.79). The ratio of E for R and S fell with decreased MBF (ER/ES=-0.05+0.12 MBF, r=0.80) and MVO (ER/ES=0.005+0.08 MVO, r=0.83).

In ischemic myocardium CPA is present in two pools, R being characterized by ß-oxidation and washout of CPA, S mainly by storage of CPA. With increasing ischemia rate and extent of ß-oxidation decreases whereas storage of CPA increases.

LEFT VENTRICULAR CONTRACTILE FAILURE FOLLOWING HYPOTHERMIC ISCHEMIC ARREST: PROTECTION BY CORONARY ARTERY WASHOUT.

Joseph T. Walls, MD; Fred Nasser, MD; David W. Baron, MD; John H. Tinker, MD; Carlos E. Harrison, MD, FACC, Mayo Foundation, Rochester, MN.

This study was undertaken to assess the value of multidose coronary artery washout (MCW) independent of cardioplegic arrest or profound hypothermia. Dogs (10±1 kg) were studied during cardiopulmonary bypass (28°C) and either 60 min (hemodynamic function, n=11) or 120 min (biochemical function, n=11) anoxic arrest. Dynamic normothermic LV function curves were generated while on right heart bypass immediately prior to anoxic arrest, and after 60 min reperfusion. Control dogs underwent simple ischemic arrest. MCW dogs had 200 ml initial (50 mm Hg, 100 ml/min, 28°C) buffered saline (pH 7.4) infused into the aortic root at cross-clamping, then 50 ml each 15 min. Results tabulated show significantly better ATP, ATP/ADP ratio, lactate concentrations at 120 mins anoxia and superior LVSW following 60 mins reperfusion. These data suggest that removal of anaerobic metabolites preserves LV contractile function following anoxic arrest independent of hypothermia.

Anoxia 28°C	120 mins. ATP (µM/g)	ATP/ADP	Lactate (µM/g)	60 mins. LVSW (g-meters)	LVEDP (mm Hg)
Control	1.67±0.16	1.84±0.15	35.6±0.6	1.2±0.05	21.8±3.5
MCW	2.19±0.13*	2.81±0.19#	19.9±2.7@	26.3±7.7+	7.6±0.4

p *0.02 #0.01 +0.001 @0.005 ±SEM

REVERSIBILITY OF DIABETIC CARDIOMYOPATHY WITH INSULIN IN RATS

Frederick Fein, MD, FACC; Ashwani Malhotra, PhD; John E. Strobeck, MD, PhD; Joseph M. Capasso, PhD; James Scheuer, MD, FACC; Edmund H. Sonnenblick, MD, FACC, Albert Einstein College of Medicine, Bronx, New York

Streptozotocin (Sz) induced diabetes (D) in Wistar rats causes a depressed force-velocity relation and slowed relaxation in isolated left ventricular papillary muscle. Actomyosin (AM) ATPase activity is also lower in D rats. The effects of insulin (4-5 units SQ/day) on these parameters were observed. Rats made D with Sz were treated 6-9 weeks later for 10 days (D+I) and compared with untreated D and controls (C). Three D rats, treated for 2 days, had normal [Glu] but all other values unchanged from D rats.

	C(n=13)	D(12)	D+I(13)
[Glu] mg%	140±5[1,2]	643±22	61±9[2]
Body wt (g)	242±4(12)[2]	197±5	242±3[2]
Heart wt (g)	.63±.01[2]	.57±.01	.73±.01[2]
DT (g/mm)[3]	4.95±.64[4]	5.81±.55	5.73±.48[4]
T1/2R (msec)[4]	101±4[2]	144±7	108±4[2]
Vs	.79±.03[2]	.63±.03	.77±.03[2]
AM ATPase[6]	.618±.007(8)[2]	.253±.015(8)	.525±.024(8)[2]

[1]Mean ± SEM, [2]p < .05 (comparison with D), [3]Max isometric [5]developed tension, [4]Time from DT to fall to 1/2 DT, [5]Peak shortening velocity at total load 45% of total isometric tension (lengths/sec), [6]µmoles Pi/mg protein/min.

These results indicate that the cardiac abnormalities induced by Sz diabetes in the rat are largely reversible with insulin.

TUESDAY, MARCH 17, 1981
AM
EXERCISE PHYSIOLOGY AND TESTING
8:30-10:00

PROGNOSIS OF PATIENTS WITH CORONARY ARTERY DISEASE BY EXERCISE TESTING

Donald A. Weiner, MD, FACC; Carolyn H. McCabe, BS; Sally S. Cutler, BS; Thomas J. Ryan, MD, FACC, Boston University Medical Center, Boston, MA

To assess whether exercise testing could help predict cardiac mortality, we analyzed 14 exercise and 10 clinical variables in 292 patients treated medically, who underwent treadmill exercise testing and cardiac catheterization. All patients were followed annually for up to 4 years. There were 13 cardiac deaths (4.5%). By multivariate discriminant analysis, the most important prognostic variables were: treadmill time, duration of ST depression, peak systolic blood pressure and cardiac enlargement. Although many of the individual clinical and exercise variables analyzed were frequently abnormal in those patients who died (sensitivity range 46% to 92%), none could accurately predict cardiac mortality (predictive value range 10-30%).

Combinations of variables were then analyzed in the subset of patients with multivessel coronary disease (n=113) whose total cardiac mortality was 11%. A high risk subgroup (n=59) consisting of patients with either severe exercise ischemia ($\geq$ 2mm ST depression lasting $\geq$ 5 minutes involving $\geq$ 3 leads) or left ventricular dysfunction (treadmill time $\leq$ 3 minutes or cardiac enlargement) had a mortality of 19% (11/59); this was significantly greater ($p < 0.01$) than a low risk subgroup (n=54) with neither severe exercise ischemia nor left ventricular dysfunction whose mortality was 2% (1/54).

We conclude that combining clinical and exercise variables to distinguish high and low risk subgroups of patients with similar coronary anatomy is useful in predicting cardiac mortality.

ERRORS OF ESTIMATION OF FUNCTIONAL CAPACITY IN CARDIAC PATIENTS

Henry S. Miller, Jr., MD, FACC; Kenneth S. Jago, MA; Paul M. Ribisl, PhD; W. Thomas Boone, PhD, Bowman Gray School of Medicine, Winston-Salem, NC

It is common practice to use standard tables in estimating the maximal functional capacity of patients from the results of a graded exercise test. The estimated values are based upon the oxygen requirement of the task while measured values, using standard gas analysis methods, reflect the oxygen delivered. To determine whether significant differences exist between estimated and observed values, 230 cardiac patients were measured on oxygen uptake during a graded exercise test on a treadmill which started at 1.7 METs and increased by 1.0 METs every second minute until a symptom-limited endpoint was reached. It was found that significant ($P < 0.05$) differences occurred at all stages above 5 METs and the disparity widened with further increments in workload. When the sample was divided into four separate groups by diagnosis (anterior myocardial infarction, inferior myocardial infarction, coronary artery bypass surgery and other) no significant ($P > 0.05$) differences among groups were observed. Similarly, three different criteria for test termination (fatigue, ECG changes or angina pectoris) failed to reveal any significant differences among groups. In conclusion, the use of standard tables overestimate the measured functional capacity of cardiac patients by 18 to 33 percent at workloads requiring from 5 to 8 METs, respectively. A regression line was developed which accurately estimates the true measured values with a standard error of $\pm$ 0.12 METs. It is recommended that the standard tables be appropriately adjusted to improve the safety and accuracy of prescription in cardiac patients for vocational and/or recreational activities.

EFFECT OF RATE-DEPENDENT LEFT BUNDLE BRANCH BLOCK ON LEFT VENTRICULAR EJECTION FRACTION AND REGIONAL WALL MOTION

Dean A. Bramlet, MD, Kenneth G. Morris, MD, David Albert, AB, R. Edward Coleman, MD, Frederick R. Cobb, MD, Duke University and VA Medical Centers, Durham, N.C.

The effect of rate-dependent left bundle branch block(RD LBBB) on LV function is unknown. To determine prospectively the independent effect of RDLBBB on LV ejection fraction(EF) and regional wall motion(WM), 6 patients with RDLBBB were selected on the basis of normal coronary arteriograms or normal thallium scintigrams obtained at maximum heart rates. The critical heart rates for developing RDLBBB were determined by preliminary upright bicycle exercise. Multigated radionuclide angiograms in the left anterior oblique view then were obtained during a second exercise. Serial measurements of LV function were made at rest, immediately before and after onset of RDLBBB, and at peak exercise. Regional WM was determined for 6 LV wall segments(2 inferoapical, 2 posterolateral, 2 septal) for each acquisition. The critical heart rate(HR) for developing RDLBBB was 113±23 beats/min (mean ± SD) which averaged 30 beats/min below peak heart rate. Mean(± SD) responses in EF and HR were as follows:

	Rest	Pre LBBB	Post LBBB	Peak
HR	77±10	108±20	114±21	145±14
EF	64±10	68±7	61±7	67±11

Regional WM in each case was normal preceding RDLBBB. With onset of RDLBBB each patient developed LV asynchrony with delayed apical contraction. Hypokinesia developed in 7 LV segments(5 inferoapical, 1 posterolateral, 1 septal) in 4 patients (66%).

Conclusion: in normal subjects during exercise the development of RDLBBB results in an abrupt decrease in LVEF, asynchronous LV contraction, and often regional areas of hypokinesia. A small overall increase in LVEF occurs despite development of RDLBBB if exercise is carried to peak levels.

EFFECT OF ANTIHYPERTENSIVE MEDICATIONS ON PHYSICAL WORK CAPACITY

Richard S. Crow, MD; George Sopko, MD; David R. Jacobs, PhD; Henry L. Taylor, PhD; Robert Serfass, PhD; University of Minnesota, Minneapolis, MN.

Cardiopulmonary fitness (MVO_2) is routinely estimated from submaximal work pulse rate (HR). Propranolol is known to reduce exercise HR and invalidates regression estimates of MVO_2. This study examines the influence of 4 additional antihypertensive medications (M) on MVO_2 prediction by measuring oxygen uptake (VO_2) and HR during submaximal and maximal exercise testing of 20 non-hypertensive males aged 20-30. Five M treatments assigned by double blind randomization were: 1) Hydrochlorothiazide (H) 50 mgs/d; 2) H + Aldomet 10 mgs/kg/d; 3) Chlorthalidone 50 mgs/d + Reserpine 0.1 mgs/d; 4) Hydropres one/d + Hydralazine 0.50 mgs/kg/d and 5) Placebo (P). We exercise tested all men in a baseline period (BL), 2 weeks on M and 3 weeks post (PM). Results: All men completed study. M adherence was 99%. No M was associated with a statistically significant decrease in rest diastolic blood pressure when compared with P, but M 2 and 3 were associated with a statistically significant decreased exercise systolic blood pressure compared with P (-19 and -22.5 mmHg). Two-way analysis of variance, allowing for a period and drug effect, showed no statistically significant effect on MVO_2 ml/kg/min. or regression estimates of Δ HR at fixed VO_2 for any M compared with P adjusted for BL response (maximum Δ HR was -7, SE diff. 5.4). We conclude from these data short-term M administration does not confound estimates of MVO_2 from submaximal HR. Further confidence in M induced Δ HR could be gained by larger sample, e.g. 85 is the estimated number of men needed to establish the significance of the observed $\pm$ 7 Δ HR at α = .05 and β = 85%.

DIGITALIS AND EXERCISE TESTING, A FIVE YEAR FOLLOWUP.
M.H. Sketch, F.A.C.C., S.M. Mohiuddin, F.A.C.C., A.Mooss, F.A.C.C., and C.K. Nair, Omaha, Nebraska

To evaluate the influence of digitalis on the results of exercise testing and the prognostic significance of digitalis induced false positive tests, 98 healthy men, 22-70 years, were studied. All had normal initial exercise tests. All took digoxin 0.25mg daily for 14 days. Subsequently, repeat daily exercise tests were performed until a negative test was obtained. Five years later, 76 men had a repeat exercise test. Medical history was obtained from 92 subjects. Six were lost to follow-up. Twenty five percent of men (24 of 98) had digitalis induced positive tests. There was a direct relationship between age and the incidence of falsely positive tests ($P=<0.03$). The incidence over age 60 years was 100% (5 of 5). Digitalis blood levels did not correlate with positive tests. The maximum ST depression induced by digitalis and exercise was 1.9mm. No test remained positive more than 12 days after discontinuing digitalis. No men developed symptomatic ischemic heart disease. Five had borderline or positive exercise tests at followup. Four of these had had digitalis induced positive tests initially.

It is concluded: 1) Patients receiving digitalis are likely to have false positive exercise induced changes especially over age 60 years. 2) Twelve days after discontinuing digoxin, results of exercise testing can be relied upon. 3) In the absence of heart disease, digoxin induces only moderate ST depression. 4) A positive test induced by digitalis does not predict subsequent 5 year morbidity and mortality. 5) The incidence of digitalis induced false positive exercise tests correlates directly with age and abnormal tests at followup. Hence, digitalis may "unmask" an age related pathology eg. coronary artery stenosis.

TUESDAY, MARCH 17, 1981
AM
CARDIAC SURGERY—1
8:30-10:00

EFFECT OF DOPAMINE AND DOBUTAMINE ON REGIONAL BLOOD FLOW, MYOCARDIAL OXYGEN CONSUMPTION AND HIGH ENERGY PHOSPHATE COMPOUNDS DURING CARDIO-PULMONARY BYPASS
Stanley Einzig, MD; John E. Foker, MD; Herbert B. Ward, MD; Richard W. Bianco, Barbara Borgwardt, Tingchung Wang, PhD; University of Minnesota, Minneapolis, Minnesota

Catecholamines are clinically important in the treatment of low CO following cardiopulmonary bypass (CPB), but questions remain on the net consequences for the stressed myocardium and the circulation. Dogs were placed on CPB, subjected to 20 min of warm global ischemia and supported for 20 min on CPB. Either 10 ug/kg/min of dopamine (Dp) or dobutamine (Db) was used as a continuous infusion for 10 min to wean the dogs from CPB and support them for 60 min off CPB. Regional blood flow (BF)(15 um radio-labeled spheres), myocardial oxygen consumption (MVO_2) and high energy phosphate levels were measured 5 min prior to coming off CPB and 60 min off CPB. Both drugs promptly altered tissue BF patterns without changing pump flow and gave the following results on CPB:

	MVO_2 (ml/min/g)	LVBF (ml/min/g)	LV Endo/Epi Ratio	Renal BF (ml/min/g)
Control (n=7)	0.03±0.02	0.62±0.05	0.94±0.04	5.56±0.32
Dopamine (n=9)	0.19±0.02	1.50±0.17	0.94±0.04	5.16±0.41
Dobutamine (n=8)	0.15±0.03	2.06±0.36	0.82±0.06	2.55±0.48

Both drugs, as expected, increased MVO_2, left ventricular BF and cerebral BF, but renal BF fell with Db. Post CPB, CO with Dp (94±5 ml/min/kg) or Db (148±15 ml/min/kg) exceeded control (66±7 ml/min/kg), cerebral and renal BF equalled control levels, and MVO_2 remained elevated. The changes in high energy phosphate levels were similar to control during and following CPB. In summary, (1) both drugs increased myocardial BF, indicating oxygen supply was meeting the increased demand, and suggesting benefit in coming off CPB; (2) on CPB, Db reduced renal BF; (3) off CPB both drugs were effective in increasing CO and maintaining renal BF, while meeting myocardial oxygen demand.

EFFECT OF VERAPAMIL ON EXERCISE-INDUCED REGIONAL MYOCARDIAL DYSFUNCTION IN CONSCIOUS DOGS.
Genta Osakada,MD; Toshiaki Kumada,MD; Kim P. Gallagher, Ph.D; W.Scott Kemper, MSEE; John Ross, Jr., MD, FACC. Univ. of California, San Diego, La Jolla, California.

The effect of verapamil (V) on exercise-induced myocardial dysfunction was evaluated in 9 conscious dogs in which ultrasonic crystals were placed for measuring wall thickness (WTh) in control (C) and ischemic(I) regions. An ameroid constrictor and an ultrasonic doppler flow probe were positioned on the circumflex coronary artery (CCA). At 23 days (average) postoperatively, complete cessation of CCA flow was confirmed by the flowmeter. Treadmill exercise was then performed for 3.8 min. at a speed of 7.5 MPH and grade of 5.3% (average), and two hours later the same exercise bout was repeated after verapamil (160 mg, P.O.):

	Before V		After V	
	Rest	Run	Rest	Run
Heart rate (beats/min)	101	243**	114	221**#
LV systolic pressure(mmHg)	130	166**	127	168**
CWTh End-diastole (mm)	10.0	10.3	10.1#	10.3
% thickening	22.4	23.8	22.1	25.7
IWTh End-diastole (mm)	10.0	10.3*	10.3#	10.6
% thickening	19.6	5.9**	17.6#	11.5**##

% thickening: percent wall thickening during systole.
*P<0.05,**<0.01: comparison between rest and running.
#P<0.05,##<0.01: comparison, before and after V.

During control running, severe regional dysfunction was observed in I zone (average % decrease in systolic WThickening = 73±7%, SEM). After V, regional dysfunction during running was markedly improved (% decrease in WThickening = 34±12%). Thus verapamil lessened exercise-induced ischemia in the collateral dependent bed, an effect which may relate to decreased heart rate and O_2 demand, improved collateral blood flow, or both.

ENHANCED MYOCARDIAL PRESERVATION IN ANIMALS AND MAN WITH NIFEDIPINE AND CARDIOPLEGIA
Richard E. Clark, MD, FACC, Ignacio Y. Christlieb, MD, Thomas B. Ferguson, MD,FACC, Clarence S. Weldon, MD, FACC, and Burton E. Sobel, MD, FACC, Washington University, St. Louis, Mo.

To characterize efficacy of a clinical cardioplegic solution (CPS) supplemented with a calcium antagonist, nifedipine (N), 30 dogs subjected to 1, 2, and 3 hrs of hypothermic (18°) global ischemia (I), were treated with aortic root bolus injection (q 30 min) of N in CPS, CPS alone or Ringer's (R). CPS + N preserved normal volume loading responses 2 hr post I and resulted in normal stroke work index(SWI) of 19 ± 2 gm·m/m^2 vs. CPS (14 ± 2) $p<0.05$ or vs. R of 10 ± 3 ($p<0.01$) at similar preloads and rates. Other indices of preserved functional and structural integrity: LVEDP, LVdP/dt, cardiac output, and histology were concordant. Subsequently, N in CPS was given to 26 Class III or IV patients (pts) (ave. age= 58 yr, 17 males) requiring an ave. of 109 min of I during bypass for single or multiple, initial or repeat valve replacement (13), CABG (7) and valve and CABG (6). Mortality by cause was comprised of uncontrollable intraoperative hemorrhage (2), late hemorrhage (1), and respirator failure (1). There were no deaths from LV failure. In contrast, a 42% incidence of postop LV power failure occurred in 31 comparable pts with similar preop ventricular function (EF <30%, CHF 82%) treated with CPS alone with a LV power failure mortality rate of 15%. Thus, nifedipine is an effective adjunct to CPS which enhances myocardial preservation in poor risk patients with complex lesions requiring extended ischemic times. Use of nifedipine has resulted in a decreased mortality and incidence of IABP support.

MECHANISM OF ACTION OF THE ENCIRCLING ENDOCARDIAL VENTRICULOTOMY (EEV) FOR TREATMENT OF INTRACTABLE ISCHEMIC VENTRICULAR TACHYCARDIA.

Ross M. Ungerleider, MD; Gary K. Lofland, MD; J. Mark Williams, MD; T.E. Stanley, BA; Raymond E. Ideker, MD, PhD; William H. Smith, PhD; James L. Cox, MD, Duke University Medical Center, Durham, North Carolina 27710.

The Encircling Endocardial Ventriculotomy (EEV) has been applied in over 50 patients for the treatment of intractable ischemic ventricular tachycardia and has been successful in 100% of survivors (operative mortality=15%). Previous studies from our laboratory have demonstrated that the EEV may isolate ventricular tachycardia from the remainder of the heart, but more often it ablates the region from which the reentry circuit originates. The purpose of this study was to clarify the relationship between the electrophysiologic and regional myocardial blood flow (RMBF) alterations induced by the EEV. Twenty-eight dogs underwent an EEV while on cardiopulmonary bypass. Bipolar and unipolar data were recorded from epicardial plaque and intramural plunge electrodes and were correlated with RMBF using radioactive tracer microspheres. The subendocardium within the EEV demonstrated a 60-70% decrease in blood flow (vs. control) and acute loss of all local electrical activity in 41.6% (20/48) of subendocardial electrograms. Outside the EEV, RMBF increased and normal local electrical activity persisted in all intramural electrograms(102/102) Within the EEV, the diastolic pacing threshold was increased from 0.31±0.03 mA before the EEV to 0.89±0.19 mA after the EEV ($p<0.002$). Pacing thresholds outside the EEV were unchanged by the surgery. These data suggest that the EEV ablates reentrant ventricular tachycardia by making the encompassed myocardium more uniformly ischemic, thereby altering the local anatomic-electrophysiologic substrate such that reentry circuits can no longer be maintained.

THE COMPARATIVE EFFECTS OF INTERMITTENT ISCHEMIC ARREST AND POTASSIUM CARDIOPLEGIA ON DIASTOLIC VENTRICULAR COMPLIANCE IN PATIENTS

W. Randolph Chitwood, Jr., MD; Ronald C. Hill, MD; James D. Sink, MD; Craig O. Olsen, MD; Andrew S. Wechsler, MD, Duke and Veterans Administration Medical Centers, Durham, North Carolina 27710

Left ventricular diastolic properties were examined in 24 patients undergoing coronary grafting using either 32°C intermittent ischemia (IA) or 4°C potassium cardioplegia (CP). Patient groups had similar ages, cardiac function, and number of grafts. For compliance data, hearts were filled passively during bypass perfusion to diastolic pressures (P) between 0 and 20 mmHg while minor axis dimensions were measured by epicardial ultrasonic crystals. End-diastolic lengths (EDL), normalized to a Lagrangian strain definition (ε), were compared by the non-linear equation, $P=\alpha(e^{\beta\varepsilon}-1)$. Both elastic constants, α and β, as well as linear regression slopes (k) of P-ε data were compared as indices of ventricular stiffness. Prior to determinations, the EDL at 0 mmHg P was defined as ℓ_o. Mean data are shown as ε at specific filling P:

*p < .01

N=12	ℓ_o(mm)	ε5	ε10	ε15	ε20	k
Pre IA	52.5	.067	.121	.142	.163	8.2
Post IA	53.0	*.049	*.083	*.098	*.116	*11.4
N=12						
Pre CP	48.0	.048	.091	.115	.140	7.9
Post CP	48.0	.037	.090	.115	.132	9.1

In these patients α, β, and k were altered by IA but not CP. Therefore, stiffening did not occur with CP despite ischemic durations twice those of IA. These data confirm CP to be a superior method of cardiac protection during coronary bypass procedures and show diastolic ventricular properties to be a sensitive indicator of subclinical ischemic injury.

INCREASE IN REGIONAL MYOCARDIAL PERFUSION POST-CORONARY ARTERY BYPASS GRAFTING.

Steven Goldman, MD, FACC; Robert Henry, MD; Mark J. Friedman, MD, FACC; Theron Ovitt, MD; Alan Rosenfeld, MD; Neal Salomon, MD; Jack Copeland, MD. Tucson VA Medical Center and University of Arizona, Tucson Arizona.

The objective of coronary artery bypass grafting (CABG) is to increase blood flow to ischemic areas of the myocardium. To determine if this was achieved, anterior wall myocardial perfusion was measured at rest and during intracoronary papaverine (5 mg), utilizing Xenon-133 washout in 35 patients (pts). Twelve control pts had no significant diameter narrowing (0-25%) of the left anterior descending coronary artery (LAD), 13 pts had >50% narrowing of the LAD, and 10 pts had >50% narrowing of the LAD with patent saphenous vein bypass grafts to the LAD and were studied 11.3±3.1 months post CABG. There was no significant difference in age, LVEDP, global ejection fraction (EF) or segmental area EF between the patients except that the controls had an increased antero-basal area EF compared to the other pts. There was no significant difference in anterior wall myocardial perfusion at rest between controls (61.0±3.7 ml/min/100g) and unoperated LAD pts (60.2 ±5.4 ml/min/100g), or operated LAD pts (63.4±4.8 ml/min/100g). During coronary arteriolar vasodilatation with papaverine, anterior wall perfusion increased in the operated pts to 140.6±6.8 ml/min/100g. This was significantly greater ($p<.001$) than the increase in the unoperated LAD pts (72.8±8.1 ml/min/100g) but not different than the increase in the controls (145.3±8.4 ml/min/100g). These data indicate that in pts with coronary disease, increases in myocardial perfusion are limited by the resistance of the proximal stenosis independent of vasodilatation distal to the stenosis. After successful CABG, the patent vein graft restores control of myocardial perfusion to the arteriolar bed.

COMPARISON OF TECHNIQUES FOR INTRAAORTIC BALLOON INSERTION

Charles E. Bemis, MD, FACC, Eldred D. Mundth, MD, FACC, Gary S. Mintz, MD, FACC, A-Hamid Hakki, MD, Abdulmassih S. Iskandrian, MD, FACC, Demetrios Kimbiris, MD, FACC, Inder Goel, MD, Margaret Riddle, RN. Cardiovascular Institute, Hahnemann Medical College and Hospital, Philadelphia, PA.

Percutaneous insertion of (Datascope) intraaortic balloon (IAB) was attempted in 44 patients (pts) between January and August 1980. The indications were: unstable angina (26 pts), severe LV dysfunction (6 pts), acute ventricular septal defect or mitral regurgitation (4 pts), and postoperative low CO (8 pts). Successful insertion was rapid, less than 15 minutes in 40 pts (91%) and was performed at bedside in 31 pts (70%). Unsuccessful attempts in 4 pts (9%) occurred in our earlier experience (4 of the first 15 pts). The use of the long (16") sheath instead of the regular sheath (7") has obviated the occasional difficulty in maneuvering the stiff IAB beyond the aortic bifurcation. Pts were not excluded because of claudication if a femoral pulse was present. The duration of counterpulsation was 1 to 9 days. After removal, hemostasis was obtained with firm pressure for 10-30 min. Two pts (5%) developed thrombosis of the femoral artery and required embolectomy; there were no other complications. Satisfactory augmentation was accomplished in all successful insertions. Doppler pedal pressures were measured in 10 pts and were unchanged after IAB. In the previous 18 months IAB insertion, via arteriotomy, was attempted in 95 pts with 15 failures (16%). There were 18 complications (19%) including limb ischemia, infection and delayed wound healing. We conclude: percutaneous IAB insertion (1) can be performed quickly at the bedside, (2) has a high success rate particularly with the long sheath, (3) has a lower rate of complications ($p < .01$), (4) does not require the surgical expertise to perform a femoral arteriotomy. The percutaneous route is the method of choice for IAB insertion.

TUESDAY, MARCH 17, 1981
AM
ACUTE MYOCARDIAL INFARCTION: I. ASSESSMENT OF ACUTE PHASE; II. ASSESSMENT IN CHRONIC PHASE
8:30-10:30

VASCULAR DETERMINANTS OF EARLY RECURRENT MYOCARDIAL INFARCTION

Alon Marmor, MD; Philip A. Ludbrook, MD, FACC; Burton E. Sobel, MD, FACC; and Robert Roberts, MD, FACC, Washington University, St. Louis, Missouri

To define coronary vascular determinants of the high incidence (43%, n=58) of early recurrent infarction (ERI) reported recently in patients with subendocardial as opposed to transmural myocardial infarction (MI) (8%, n=132) we evaluated coronary angiograms in 73 patients in whom initial MI was subendocardial in 33 and transmural in 40. Coronary angiograms were obtained within 48 days. In 17 patients, ERI developed, averaging 10 ± 4 (SD) days after the initial MI, all of whom initially had subendocardial MI. None of the patients with transmural MI exhibited ERI. The ECG site of recurrent MI was concordant with the site of the initial MI in every case. Coronary stenosis exceeding 75% was present in all patients. However, incomplete occlusion was evident in 74% of patients with subendocardial but in only 17% with transmural MI. In patients with subendocardial MI and incomplete coronary occlusion, 58% (14/24) developed ERI compared to only 10% with complete occlusion. Thus, incomplete occlusion is strongly associated with subendocardial MI, a progenitor of ERI. Recurrent infarction was frequently associated with ST elevation resembling that seen in variant angina (71%). In concert the data suggest that coronary spasm superimposed on fixed obstruction is implicated in the genesis of ERI because: 1) ERI is generally presaged by subendocardial MI which in turn is associated with incomplete coronary occlusion; 2) ERI is manifested by ST segment elevation rather than depression; and 3) the ECG locus of the recurrent infarction is concordant with that of the initial infarction with both a reflection of the locus of the angiographically delineated fixed obstruction.

MYOCARDIAL INFARCT EXTENSION: DIAGNOSIS, INCIDENCE, AND CLINICAL SIGNIFICANCE.

Hans D. Strauss, MD, FACC; Ian L. Macdonald, MD; Sally A. Orr; Neil D. Berman, MD, FACC; Andrew J. Buda, MD, FACC, University of Toronto, Toronto, Canada.

The incidence, methods of detection, and consequences of extension (Ext) after myocardial infarction (MI) remain controversial. We studied 80 patients (pts) by serial 8-hourly quantitative CK-MB and daily ECG's for 10 days post MI. There were 67 men and 13 women with a mean age of 64 years (range 44-80 yrs). Mean infarct size assessed enzymatically was 18 ±3 CK gm eq/m2. MI Ext defined by re-elevation of CK-MB, occurred in 28 (35%) at a mean of 5.8 days (range 3-10 days) post MI. MI Ext by ECG (ST segment re-elevation) occurred in 8 (10%). Resting (>15 min) ischemic chest pain (CP)occurred in 25 (32%). The sensitivity (sens), specificity (spec), and positive predictive accuracy (PPA) of ECG, CP, and total CK compared to CK-MB in detecting MI Ext were:

	Total CK	ECG	CP	ECG & CP	ECG and/or CP
sens (%)	14	18	37	33	41
spec (%)	100	87	72	96	64
PPA (%)	80	42	40	40	37

In-hospital mortality after 3 days post MI was 18% in pts with MI Ext by CK-MB compared to 2% in pts without Ext ($p < 0.01$). The risk ratio for mortality was 9.3 in pts with CK-MB Ext, 2.8 with ECG MI Ext, and 8.8 in pts with recurrent CP. No factors predictive of subsequent MI Ext were found. We conclude that MI Ext occurs frequently and is a useful predictor of mortality. ECG and CP are insensitive compared to CK-MB in diagnosing MI Ext.

MYOCARDIAL INFARCT EXTENSION: REASSESSMENT OF INCIDENCE, DETECTION, AND INFLUENCE ON SURVIVAL

John T. Baker, MD, Dean A. Bramlet, MD, Robert M. Lester, MD, David G. Harrison, MD, Charles R. Roe, MD, Frederick R. Cobb, MD, Duke University & VA Med Ctrs, Durham, N.C.

The incidence of myocardial infarct extension(MIE) as detected by precordial ST-segment mapping has been reported to be as high as 86%. Mortality attributed to MIE has varied from 8.3 to 40%. The purpose of this study was to utilize creatine phosphokinase myocardial-specific isoenzyme(CK-MB) activity, a specific serological marker of myocardial necrosis, to determine prospectively the incidence of MIE, the reliability of ST-segment changes to detect MIE, and the relationship of MIE to survival in-hospital after acute myocardial infarction. Routine 12-lead electrocardiograms and plasma CK-MB activity were measured every 12 hours for 10 days in 56 consecutive patients with acute myocardial infarction. MIE was defined as either 1) reappearance of CK-MB activity or 2) re-elevation of CK-MB activity >48 hours after onset of acute myocardial infarction. Additional or new ST-segment elevation ≥ 1 mm beyond 48 hours after onset of acute myocardial infarction was noted. MIE occurred in 14.3%(8/56 patients), a mean of 4.6 days after onset of acute myocardial infarction. CK-MB re-elevation occurred in 75%(6/8) and CK-MB reappearance in 25% (2/8). ST-segment changes occurred in 50%(4/8) of patients with MIE, but also in 45%(17/48) without MIE($p=0.34$). Late hospital mortality was 50%(4/8) with MIE vs 2.1%(1/48) without MIE($p=0.0009$).

We conclude that 1) the incidence of MIE detected by CK-MB is much lower than previously reported with ST-segment mapping, 2) recurrent ST-segment changes on standard electrocardiograms are neither sensitive nor specific indicators of MIE, and 3) MIE as detected by secondary elevation of CK-MB activity >48 hours after acute infarction identifies a subset of patients at high risk for late in-hospital death.

HEART RATE RESPONSES TO HOME ACTIVITIES SOON AFTER MYOCARDIAL INFARCTION

Lois M. Sheldahl, PhD, Nancy A. Wilke, BS, C. Vincent Hughes, MD, Felix E. Tristani, MD, FACC, Cardiopulmonary Rehabilitation Center, Veterans Administration Center and Medical College of Wisconsin, Milwaukee, WI.

Adequate data is not available on the cardiac response to home activities in myocardial infarction (MI) patients (pts) following hospital discharge. Heart rate (HR) response to home activities was determined on 40 pts who underwent 24 hour ambulatory electrocardiographic monitoring (AEM) approximately 3 weeks after MI. Detailed diaries of home activities were kept. The mean peak HR on the AEM was 106±18 bpm compared to a mean peak HR of 113±16 bpm on a low-level graded exercise test (LL-GXT) performed prior to discharge. Fifteen pts (38%) showed a higher peak HR on the AEM compared to the LL-GXT. During home activities, 25 pts (63%) exceeded their upper prescribed HR (resting + 20 bpm) for at least 10 consecutive minutes and 19 (48%) of these pts sustained this elevated HR for at least 30 consecutive minutes. Home activities associated with a HR in excess of prescribed levels included self-care morning activities (n=19), household and shopping activities (n=10), anxiety related events (n=7), and walking (n=4). Angina pectoris was rarely reported. Conclusions: 1) home activities often lead to excessive HR levels in pts 3 weeks post-MI; 2) the increased cardiac stress may be deleterious to some pts; 3) on the other hand, the sustained elevated HR during home activities may be partially responsible for the training effect reported in some post-MI pts not in exercise programs.

THE EFFECT OF EXERCISE PRESCRIPTION ON THE RECURRENCE RATE OF MYOCARDIAL INFARCTION IN MEN

Peter A. Rechnitzer, MD, FACC; Principal and Associate Investigators. The Ontario Exercise-Heart Collaborative Study. University of Western Ontario, London, Ontario, Canada.

This multi-center trial was carried out (1972-1979) to determine whether a program of endurance exercise would reduce the recurrence rate among male patients who had survived an initial myocardial infarction. The study population consisted of 733 men who were randomized into a high intensity exercise (HIE) (379) or a low intensity exercise (LIE) (354) group. Participants in the HIE group were given an individualized exercise prescription designed to produce a significant training effect, while those in the LIE group engaged in mild recreational activities structured to avoid training effect. The overall drop out was 45%. 93% of all drop-outs were followed to the completion of the study. Over the four year intervention period, the total recurrence rate for the HIE group was 9.5% and for the LIE group was 7.3%. Life-Table methods of analysis failed to reveal any significant difference in recurrence rates between the groups. The cumulative relative odds of re-infarction in the HIE group during the time of active participation were 1.24 compared to the LIE group. If re-infarctions after the date of drop-out were included, similar cumulative relative odds of re-infarction in the HIE group were 1.09 compared to the LIE group. Although the re-infarction rate was lower than expected, this study failed to demonstrate that prescribing a program of endurance training was more effective than participation in mild recreational activities in reducing the incidence of fatal and non-fatal re-infarction.

TUESDAY, MARCH 17, 1981
AM
INFLUENCE OF RISK FACTORS IN CARDIOVASCULAR DISEASE
8:30-10:00

A-B CORONARY-PRONE BEHAVIOR PATTERN AND CARDIOVASCULAR RISK FACTOR VARIABLES IN CHILDREN AND ADOLESCENTS: THE BOGALUSA HEART STUDY.

Saundra MacD. Hunter, PhD; Thomas M. Wolf, PhD; Monny C. Sklov, PhD; Larry S. Webber, PhD; Gerald S. Berenson, MD, FACC, L.S.U. Specialized Center of Research--Arteriosclerosis, New Orleans, Louisiana.

The relationship between Total score and Factors derived from a Hunter-Wolf Self-Rating Scale for children and several physiologic risk factor variables related to cardiovascular disease were analyzed as part of a larger study on children, ages 10-17, in a biracial community.

For each sex-race group, four Factor scores and the Total scores were ranked into quintiles. Children in the upper quintile were referred to as Type A children and those in the lower quintile, Type B. For Factor I, "eagergy," e.g., I walk fast, I eat fast, significant mean differences were found for serum total and β- and pre-β-lipoprotein cholesterol and triglycerides. In each instance, children classified as Type A exhibited approximately 10 mg/dl higher readings except for pre-β-lipoprotein cholesterol in which a 2 mg/dl difference was noted. Significant interaction was found between the effects of Factor I behavior, race, and sex on systolic and diastolic blood pressure. Black boys who scored in the Type A direction had higher systolic blood pressures while white Type A girls had higher diastolic blood pressures than their Type B counterparts ($p<0.05$). These observations show it is possible to identify in children behavior characteristics that relate to cardiovascular disease.

RIGHT ATRIAL PACING SOON AFTER MI: DETECTION OF RESIDUAL MYOCARDIAL ISCHEMIA AND PREDICTION OF EARLY PROGNOSIS

Dan Tzivoni, MD; Elihau Gazala, MD; Andre Keren, MD; Chaim Granot, MD; Shmuel Gottlieb, MD; Jose Golhman, MD; Shlomo Stern, MD, FACC, Bikur Cholim Hospital, Jerusalem, Israel

To assess the presence of residual myocardial ischemia and its prognostic significance, right atrial pacing (RAP) was performed in 74 consecutive post MI pts aged 29-85, the day before discharge. No pt was excluded from the study because of clinical status. RAP was performed at bedside and pacing rate was increased by 10 beats every 2 min up to 160/min. Pacing was terminated if >3mm ST depression or severe angina developed. RAP was regarded positive if >1mm ST depression developed. There were no complications. Pacing was performed 10-28 days post MI (mean=14.2). Maximal pacing rate ranged between 100-160/min (mean=148/min). Results (table): 19% of the anterior, 59% of the inferior and 68% of the subendocardial MIs were positive. Follow-up was 1 to 12 months (mean=5.8 months). Among the 39 pts with normal RAP there was 1 sudden death, no reinfarction, and 5 had chest pain. Of the 35 positives there were 3 deaths (2 reinfarctions, and 1 sudden), 5 had reinfarction and 10 had chest pain. Treadmill stress test (TT) was performed in 37 pts 6 months post MI. Of 21 with negative RAP 17 had negative and 4 positive TT; of 16 with positive RAP 12 had positive and 4 negative TT.

Conclusions: RAP can be performed safely soon after MI, is sensitive in detecting residual myocardial ischemia, it can identify pts at risk for reinfarction and probably for death. RAP predicted the presence of exercise induced ischemia 6 months after MI. RAP can be performed in all post MI pts, requires no cooperation and if ischemia develops, it can be stopped immediately.

Infarct pts		Negative		Positive	
Anterior	27	22	(81%)	5	(19%)
Inferior	22	9	(41%)	13	(59%)
Subendo.	25	8	(32%)	17	(68%)
Total	74	39	(53%)	35	(47%)

PLASMAPHERESIS IN THE TREATMENT OF CHILDREN WITH HOMOZYGOTIC TYPE II HYPERLIPIDEMIA

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Homozygotic children with Fredrickson's Type II hyperlipidemia have severe cholesterolemia and suffer early death from progressive coronary artery disease. We evaluated the use of plasmapheresis in two boys, 8 and 11 years, over a period of 5 and 11 months. Both had disfiguring tendinous and palmar xanthomata. The older boy had aortic stenosis and coronary artery disease proven by cardiac catheterization. Plasma exchange via two venipunctures was performed every two weeks on an IBM cell separator. Plasma volume equal to 6% of body weight was replaced by 5% albumen solution. Acidified citrate dextrose was used for anticoagulation. The total treatment averaged 2½ hours. BP, HR and temperature were monitored. Cholesterol (CHOL), triglyceride (Tg), HDL, total protein, PT, PTT, Ca^{++}, Mg^{++}, electrolytes, CBC, platelets, LDH, SGOT and SGPT were drawn before and after exchange. CHOL was significantly lowered by plasmapheresis. Mean CHOL in the 8 year old fell from 698 mg% to 318 mg% with an average of 5.1 gm CHOL removed per run. Mean CHOL in the 11 year old fell from 890 mg% to 384 mg% with an average of 6.3 gm CHOL removed per run. Marked regression in xanthomata occurred in both boys and no new skin lesions developed during this period. Transient decreases in Tg, HDL, TP, Hgb, SGOT, SGPT occurred immediately following plasmapheresis, but levels returned to normal by the next treatment. No significant changes were seen in platelet count, Ca^{++}, Mg^{++} or electrolytes. PT and PTT became prolonged following the exchange, but were normal at the next treatment. No incidents of hypotension, tachycardia, temperature elevation, or bleeding diathesis occurred during or after therapy. Plasmapheresis lowers CHOL in the child with severe hypercholesterolemia and is well tolerated.

BLOOD PRESSURE RELATED ECHOCARDIOGRAPHIC CHANGES IN ADOLESCENTS AND YOUNG ADULTS. Gregory L. Johnson, M.D., FACC., Carol M. Cottrill, M.D., FACC., Harley E. McKean, Ph.D., J. Morley Kotchen, M.D., University of Kentucky, Lexington, KY.

Of 873 adolescents screened for the presence of hypertension during high school, 126 were evaluated by blood pressure (BP) measurement and echocardiography five years later. The 126 subjects included the upper and lower 5th percentile for blood pressure at the time of initial screening and a random control sample selected from the remainder of the population. Systolic and diastolic BP measurements performed at followup were highly correlated ($p < .002$) with initial values and ranged from 94-188 systolic and from 42-106 diastolic. Echographic exam demonstrated that when results were corrected for differences in body mass, there was no relation between either systolic or diastolic BP and LV chamber dimensions, septal thickness, LV wall diastolic thickness or calculated cardiac mass. Subjects with higher systolic BP did demonstrate significant ($p < .01$) increases in resting heart rate, percent fiber shortening, mean velocity of circumferential fiber shortening, LV preejection period/ejection time ratio and both degree and rate of LV systolic wall thickening. Diastolic BP correlated only with degree of systolic wall thickening. These changes were independent of body mass.

Early in the course of systolic hypertension increased work, rather than hypertrophy, appears to be the primary cardiac manifestation of elevated BP. Therapeutic intervention at this point may prevent the consequences of subsequent cardiac hypertrophy.

RELATIONSHIP BETWEEN PLASMA TESTOSTERONE AND LIPOPROTEIN CHOLESTEROL

Lewis H. Kuller, MD, James Gutai, MD, Ronald LaPorte, PhD, Lorita Falvo-Gerard, MN,MPH and Wanju Dai, MD. University of Pittsburgh, Pittsburgh, Pennsylvania

The distribution of lipoprotein cholesterol, specifically HDLc and triglyceride, is probably primarily determined by hormonal levels. We have studied the relationship between plasma testosterone, known risk factors for HDLc (exercise, obesity, alcohol intake) and the levels of lipoprotein cholesterol and triglyceride in a sample of 247 men participating in the Multiple Risk Factor Intervention Trial (MRFIT).

The free and bound testosterone levels decreased with increasing age. Besides age, the major determinant of free and bound testosterone was obesity. Also, individuals gaining weight had a decrease and those losing weight had an increase in testosterone over a one year period. The free and bound testosterone levels were both directly correlated with the HDLc levels and inversely with triglycerides. (Table below) The relationship between testosterone and HDLc and triglycerides persisted even after adjusting for obesity and other determinants of HDLc. Change in plasma testosterone levels and perhaps other hormones, secondary to lifestyle modifications, such as weight change, physical activity, and alcohol consumption may be major determinants of the HDLc distribution in the population.

	BOUND TESTOSTERONE (NG/DL) QUINTILES				
	78-533	534-641	642-761	762-936	937-1650
HDLc (MG/DL)	41	44	43	43	48
TRIG (MG/DL)	222	195	183	190	152

CIGARETTE SMOKING AND NON-FATAL MYOCARDIAL INFARCTION IN WOMEN

Charles H. Hennekens, MD; Walter C. Willett, MD; Christopher Bain, MB; Bernard Rosner, PhD; Frank E. Speizer, MD, Harvard Medical School and Brigham and Women's Hospitals, Boston, MA.

The relationship between cigarette smoking and risk of hospitalization for acute myocardial infarction (MI) was evaluated among 121,964 married, female, registered nurses who responded to a postal questionnaire. Among 249 women who experienced a first MI, 159 (64%) were cigarette smokers at the time of hospitalization. Of 4980 controls matched 20:1 to cases on the basis of age, 1850 (37%) were cigarette smokers at the corresponding time. Cigarette smokers experienced a three-fold increase in risk of MI relative to women who had never smoked (95% confidence limits from 2.3 to 4.0). This relationship was not materially altered by simultaneous adjustment using multiple logistic regression analysis for additional variables which included history of hypertension, diabetes, elevated cholesterol, and family history of MI (95% confidence limits from 2.3 to 4.3). Among current smokers there was evidence for a dose-response relationship with MI. Women who had stopped smoking experienced a risk of MI no greater than those who had never smoked.

RELATION OF EXERCISE ELECTROCARDIOGRAPHIC ST CHANGES TO PHYSIOLOGICAL MEASUREMENTS IN MEN AT HIGH RISK OF FUTURE CORONARY DEATH

Pentti M. Rautaharju, MD, FACC; Steven Broste, MS; Richard S. Crow, MD; Curt Furberg, MD; Ronald J. Prineas, MD, FACC; for the MRFIT Research Group, Dalhousie University, Halifax, Nova Scotia, Canada.

The prevalence of the ischemic response by visual analysis and the computer measurement of 3/8 ST segment integral (STI) was determined through electrocardiographic analysis of the records of 12,866 men chosen for a graded submaximal exercise test in the Multiple Risk Factor Intervention Trial (MRFIT). These men were 35 to 57 years of age and clinically free of coronary heart disease (CHD) and were identified to be in the upper 15% risk group for future CHD death. Multiple regression analysis revealed that STI during peak exercise had a statistically significant positive association with age, diastolic blood pressure, serum cholesterol and fasting blood glucose and a significant negative association with smoking, alcohol consumption, resting heart rate, serum potassium, fasting time preceding the test and body mass index. However, the association between smoking and ST depression was no longer significant when men who did not reach age-specific target heart rate were excluded from analysis. The overall prevalence of computer measured ischemic response (defined as 3/8 STI $\geq 16\mu Vs$ at peak exercise or immediate recovery with STI $<6\mu Vs$ at rest) was 12.45%. The prevalence of ischemic response in visual analysis, using conventional criteria (horizontal or down-sloping ST segment with J-point depression 0.05mV or more) in immediate or 3 minute recovery records was low (2.44%) in this population at high risk of CHD death.

TUESDAY, MARCH 17, 1981
AM
MYOCARDIAL/PULMONARY VASCULAR DISEASE
8:30-10:00

MURINE COXSACKIEVIRUS B4 CARDIOMYOPATHY; MYOCARDIAL INFARCTION AND VENTRICULAR ANEURYSMS.
Riad Khatib, M.D.; Jacob L. Chason, M.D. and A. Martin Lerner, M.D., Wayne State University School of Medicine, Detroit, Mich.

Intraperitoneal inoculation of 48 hr. old mice with 10^4 TCD_{50} Coxsackievirus B4 (Dowell) induces transmural myocardial necrosis and ventricular aneurysms in some of the survivors. The epidemiology and long-term consequences of this "cytopathic" type infection in which maximum virus titers and pathologic changes in the myocardium are synchronous has not been studied. Coxsackievirus B4 infected suckling mice (821 subjects) and sham-inoculated controls (175 subjects) were followed over a 12 month surveillance. Blood and hearts from 10 subjects each were collected (2,5,9, and 30 days; and 2,3,6,9, and 12 months) and clinical findings, ratios of hearts to total weight (HBW), histopathologic findings and neutralizing antibodies (NA) were determined. 679 infected subjects died within 30 days, and 28 more animals succumbed within the next 11 months. Only 44 of the controls died. HBW ratios in both groups were similar throughout. NA did not appear until one month and persisted thereafter. Gross evidence of myocarditis or ventricular aneuyrsms among examined subjects were (25 of 114 subjects (22.8%); 69 of 92 hearts (75%) showed myocarditis histologically. The left ventricular (64 of 69 hearts (92.7%), interventricular septum (39 of 59 hearts (56.5%) and right ventricle (26 of 69 hearts (37.5%) were affected. Transmural scars (or gross ventricular aneurysms were seen in 22 of the 69 hearts (31.8%); left ventricle (16x); I-V septum (5x); right ventricle (5x). Coronary arteries were patent, but the scars resembled myocardial infarctions.

PREALBUMIN IS A COMPONENT OF SENILE CARDIAC AMYLOID
Gibbons G. Cornwell, III, M.D.; Per Westermark, M.D.; Wendy Murdoch, B.S., Dartmouth Medical School, Hanover, NH

We have previously shown that two distinct forms of amyloid may exist in heart tissues of elderly patients. One type, known as isolated atrial amyloid (IAA) is limited to the atrium and has not yet been characterized. The other type, which contains a protein heretofore designated ASc_1, may be present in atrium or ventricle, as well as certain extra-cardiac tissues such as lung and kidney. An antiserum specific for ASc_1 has been used previously to show that this protein is not present in amyloid of the AA type, of the A_λ types or in amyloid associated with medullary carcinoma of the thyroid (MCT) or adult onset diabetes. The present studies show that an antiserum specific for human prealbumin (aHPA) reacts in immunofluorescence with senile cardiac amyloid of the ventricle in a pattern identical to that of anti-ASc_1. This antiserum fails to react with cardiac amyloid of the IAA type, primary amyloid ($A_\lambda I$, $A_\lambda IV$, $A_\lambda VI$), secondary amyloid (AA), amyloid associated with MCT (AE_t), pancreatic amyloid associated with adult onset diabetes, cerebral amyloid present in Alzheimer's disease, or lichen amyloid. The reaction of aHPA is completely blocked by purified prealbumin but is not influenced by absorption with purified human albumin or proteins from any amyloid types tested. The aHPA reaction is also totally blocked by purified protein ASc_1, and the reaction of anti-ASc_1 is similarly blocked by purified human prealbumin. These studies strongly suggest that senile cardiac amyloid of the ASc_1 type contains prealbumin or a protein immunologically identical to this molecule. This finding is similar to that reported for the heredofamilial type of amyloid which has also been reported to contain human prealbumin.

CORRELATIONS OF FIBROSIS IN LEFT VENTRICULAR ENDOMYOCARDIAL BIOPSIES FROM PATIENTS WITH AORTIC VALVE DISEASE.
Paul Oldershaw, MRCP, John Coltart, FRCP, Stephen Jenkins FRCP, Michael Webb-Peploe FRCP.

St. Thomas' Hospital, London. SE1 England.

Exercise tolerance remains poor after aortic valve replacement in patients (pts) who have impaired left ventricular (LV) function preoperatively; the reasons for this are not clear. We have assessed the role of structural changes in the myocardium in limiting postoperative exercise tolerance by measuring percentage fibrosis (PF) in preoperative LV biopsies and comparing this with 1) other data obtained at catheter and 2) with the patients clinical status at follow up. PF was measured using a standard point-counting technique. Biopsy specimens were obtained from 55 pts with aortic stenosis (mean age 59 yrs) and 42 pts with aortic regurgitation (mean age 48 yrs). Fibrosis was present in 33 (60%) of the pts with aortic stenosis and there was a significant correlation between PF and LV ejection fraction ($r = 0.72$, $p < 0.01$). Mean peak systolic gradient was significantly higher in pts with fibrosis (83±4mm Hg) than in pts without fibrosis (67±6mm Hg) ($p \leq 0.01$). By contrast, fibrosis was found in only 17 (40%) of the 42 pts with aortic regurgitation and was never severe. There was no correlation between PF and ejection fraction or degree of regurgitation. In both groups of pts (stenosis and regurgitation) there was strong correlation between PF and patients' follow up symptomatology, need for antifailure treatment and mortality. We conclude that PF may be a prognostic indicator in pts with aortic valve disease.

THE CARDIAC DISEASE OF MYOTONIC MUSCULAR DYSTROPHY.
Nigel K. Roberts, MD, FACC, William R. Cabeen, MD, FACC, and Joseph K. Perloff, MD, FACC, UCLA School of Medicine, Los Angeles, CA.

In myotonic muscular dystrophy (MMD)—a systemic disease characterized by dystrophy, myotonia and features of premature aging—the relative importance of electrophysiologic and myocardial involvement has not previously been studied in the same patient population. Accordingly, we investigated 15 subjects, 7 males and 8 females with active MMD (electromyography, biopsy, elevated CPK). Average age was 36 years. Males were less than 40 years. Females were premenopausal. No patient was diabetic. Average disease duration was 15 years. Cardiac symptoms were confined to palpitations in 4/15. Cardiac electrical activity was studied by electrocardiography, vectorcardiography, ambulatory monitors and intracardiac multiple electrode catheters. Ventricular function, wall motion and chamber size were studied by M mode and 2 D echocardiography, and technetium (^{99m}Tc) radionuclide angiocardiography. Results: left anterior fascicular block (LAFB) 8/15; supraventricular tachycardia 3/15 (2 triggered); ↑ sinus node recovery time 2/15; ↑ atrial refractory period 5/15; ↑ AV node conduction 1/15 (with atrial pacing); ↑ HV conduction 8/15, borderline 2/15 (55 msec), normal in 2/15 with LAFB; entirely normal studies 2/15. Pharmacologic denervation yielded no increase in abnormalities. ^{99m}Tc angiocardiography: ejection fraction (EF) 50-73% (av 58); wall motion normal (no dystrophy or myotonia). Echocardiography: EF 50-80% (av 67); % fractional shortening 30-48 (av 34), chamber size and wall motion normal. Conclusions: Cardiac disease in MMD selectively disturbs impulse formation and conduction, especially infranodal, with no detectable abnormalities of contraction. The electrophysiologic abnormalities resemble those of aging, and may be yet another feature of the progeria of MMD.

THE NATURAL HISTORY OF IDIOPATHIC PULMONARY HYPERTENSION
Valentin Fuster, MD, FACC; Emilio R. Giuliani, MD, FACC; Robert O. Brandenburg, MD, FACC; William H. Weidman, MD, FACC; William D. Edwards, MD, FACC, Mayo Clinic, Rochester, Minnesota

The study comprises 100 consecutive patients (pts) with idiopathic pulmonary hypertension (IPH) by clinical and hemodynamic criteria and followed up for a median of 10 years (yrs) (range 4-24). The initial clinical manifestation was dyspnea (78 pts), exertional dizziness (15 pts), fatigue (4 pts), exertional chest pain (3 pts). At diagnostic study, the average pulmonary artery pressure was 96/43 mm Hg (range 51-208/25-107). Seventy-four pts were female and 26 males. Median age was 30 yrs (range 2-70) at the time of first clinical manifestation and 33 yrs (range 3-70) at the time of diagnostic study. The incidence of thrombophlebitis (6 pts) and of the use of oral contraceptives (13 pts) did not appear to differ from that in the general population.

From the time of hemodynamic diagnosis, 91 pts were dead at a median interval of 2 yrs and 9 pts had survived for at least 4 yrs. From analysis of all probable predictive clinical and hemodynamic factors, only the use of anticoagulants (A/C) initiated at the time of diagnosis in 36 pts appeared to show a beneficial trend; of the 9 survivor pts, 5 were taking A/C; in the nonsurviving pts who had been taking A/C (31 pts) average survivorship was 1 yr longer.

In summary, this large and long-term followup study on IPH revealed that this disease predominates in young women, it is diagnosed when the disease is already too advanced, and its course to death is very short. Anticoagulants may be of benefit, but usually are initiated too late in the course of the disease.

COMPARATIVE HEMODYNAMIC AND CLINICAL RESPONSES TO ISUPREL, DIAZOXIDE AND HYDRALAZINE IN SEVERE PRECAPILLARY PULMONARY HYPERTENSION
Charles R. McKay, MD; Kanu Chatterjee, MB, FRCP, FACC; Gilbert L. Raff, MD; Bruce H. Brundage, MD, FACC; William W. Parmley, MD, FACC, University of California, San Francisco, Ca.

Acute resting hemodynamic responses to Isuprel (I) (0.5 to 2.0 µg/min.I.V.), hydralazine (H) (25 to 100 mg. p.o.) and diazoxide (D) (50 to 350 mg. I.V.) were determined in 7 patients (PTS) with severe precapillary pulmonary hypertension (PPH). No drug had significant beneficial effects on mean pulmonary artery pressure (PA) or total pulmonary resistance (TPR) for the entire group of PTS. All 3 drugs significantly increased cardiac output (CO), primarily due to increased heart rate (HR). I and D significantly decreased total systemic resistance (TSR) without decreasing TPR. Control = C; Therapy = T

	HR (beats/min.)		CO (L/min./m^2)		PA (mm.Hg)		TPR (dynes.sec.cm-5)		TSR	
	C	T	C	T	C	T	C	T	C	T
I	85†	104	4.1	5.8†	55	66	1055	985	1855	1377*
H	93	99	4.6	5.3**	62	63	1207	1107	1700	1404
D	94	100	3.8	5.1††	53	54	1012	950	1899	1432**

p <.05*, p <.025**, p <.005†, p <.001††

Four of the 7 PTS had decreased PA pressure or TPR associated with increased stroke volume, and were continued on oral H (2 PTS) or D (2 PTS). One PT continues symptom free at 10 months on D. Three other PTS had drug related complications preventing long term therapy. Limited improvement and adverse effects of acute and chronic therapy caution against the empirical use of these drugs in PPH without hemodynamic documentation of their efficacy in individual PTS.

TUESDAY, MARCH 17, 1981
AM
EXERCISE TESTING
10:30-12:00

THALLIUM-201 MYOCARDIAL PERFUSION IMAGING IN WOMEN: CORRELATION WITH CORONARY ARTERIOGRAPHY
William Ceretto MD FACC, Victor Vieweg MD FACC, Robert Slutsky MD. Naval Regional Medical Center and University of California, San Diego

Thallium-201 myocardial perfusion imaging (MPI) has been shown to be a sensitive and specific technic in the diagnosis of coronary artery disease (CAD) in men. While the difference between treadmill sensitivity for CAD in men and women is well known, as yet similar data are not available for MPI. Thus we utilized stress and reperfusion MPI in 30 female patients with chest pain prior to coronary arteriography.

	+THALLIUM	-THALLIUM
+ CAD (n=13)	4 (31%)	9 (69%)
- CAD (n=17)	3 (18%)	14 (82%)

In general, pts with CAD and negative scintigrams had a lower peak exercise heart rate (68.7+ 10.5% predicted vs. 83.3 + 13% predicted $p < .05$) than pts with CAD who had perfusion abnormalities. Of the 9 pts with false negative studies, 7 were ingesting propranolol, 6 long acting nitrates, and 6 did not reach 80% of their predicted heart rate. One had single vessel disease. Three subjects had false positive studies, two had mitral valve prolapse and one had diabetes mellitus and a positive treadmill ECG response. Thus in this study, the sensitivity of thallium MPI was poor (31%) and the predictive accuracy of a positive test low (61%), although any number of factors may have influenced the results. We thus conclude that thallium-201 MPI in women with chest pain is limited in utility, particularly in subjects with mitral prolapse or those ingesting propranolol.

EXERCISE TESTING OF WOMEN WITH CHEST PAIN WITH AND WITHOUT THALLIUM TOMOGRAPHY
Ivan Pacold, MD; Paul T. Maier, MD; John F. Moran, MD, FACC; David J. Hale, MD, FACC; Robert Henkin, MD; Rolf M. Gunnar, MD, FACC, Loyola University Medical Center, Maywood, Il and Hines VA Hospital, Hines, Il

Women with angina-like chest pain frequently develop falsely abnormal ST segment depression on multistage exercise testing (MET). Ninety-six female patients (pts) with chest pain were studied with MET and coronary angiography. ST segment depression of 1 mm or more on exercise and 50% or more reduction in diameter of any coronary artery were considered abnormal.

MET was abnormal in 40 of 96 pts. Thirty of these 40 pts had normal coronaries. MET was normal in 56 of 96 pts. Forty-nine of these 56 pts had normal coronaries. The sensitivity of MET was 58% and specificity 62%. Analysis by duration of exercise (3 min or longer) or by maximal systolic BP (130 mmHg or higher) did not improve these findings.

Additional 32 pts were studied with MET, coronary angiography and with stress/rest thallium planar and seven pinhole tomographic images. Reversible and irreversible defects on thallium scans were considered abnormal.

The thallium scan was abnormal in 17 of 32 pts. Five of these 17 pts had normal coronaries. The thallium scan was normal in 15 of 32 pts. Ten of these 15 pts had normal coronaries. The sensitivity of the thallium scan was 71% and specificity 67%.

Although the thallium scan may be more sensitive than MET in the detection of coronary disease in women, the usefulness of MET and the thallium scan in the evaluation of women with chest pain is limited by the low specificity of either test in this patient population.

ABNORMAL BLOOD PRESSURE RESPONSE DURING AN EXERCISE TEST

Ricardo Bessoudo, MD; Robert N. Anderson, MD, FACC; Dalhousie University, Halifax, Nova Scotia, Canada.

Patients (pts) with coronary artery disease (CAD) in contrast to normals (N), have less increase or a fall in systolic (SYS) blood pressure (BP) during exercise (EX). In order to assess the BP changes during early recovery (R) from EX, we studied 130 pts, 104 males and 26 females (mean age 52 years) who underwent a submaximal bicycle EX test (T) prior to coronary arteriography. BP was recorded during all stages of EX and R. Critical CAD ($\geq$70% luminal narrowing) was present in 88 pts: 26 with 1 vessel disease (1VD); 30 with 2 vessel disease (2VD); and 32 with left main or 3 vessel disease (LM-3VD). 42 were N.
Of the 130 pts, 90 had a fall in BP during the first minute of R and 40 had a rise (RI) in BP during this period. Of the pts with BP RI, 6 had 1VD, 12 had 2VD, 19 had LM-3VD and 3 were N. The sensitivity (SEN), specificity (SP) and the predictive value (PV) of SYS BP RI in R as compared to that for ECG changes (Δ) (0.1 mV. ST depression at 80 m/sec) were as follows:

	SEN%	SP%	PV%
ECG Δ	51	90	92
SYS BP RI	42	93	93

For LM-3VD, results were:

ECG Δ	72	73	47
SYS BP RI	59	79	48

Thus, SYS BP RI during the R period of an EX T is almost as useful as ECG Δ in the diagnosis of CAD.

SENSITIVITY OF EXERCISE INDUCED CHANGES IN APEX OF T TO END OF T AND QT INTERVALS FOR DETECTING CORONARY DISEASE

Jacqueline O'Donnell, MD; Suzanne B. Knoebel, MD, FACC; D. Eugene Lovelace, BS; Paul L. McHenry, MD, FACC, Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana

Exercise-induced myocardial ischemia may result in nonhomogeneous repolarization which is reflected as changes in the QT and apex of T to end of T (aT-eT) intervals. We have studied the sensitivity and specificity of the aT-eT interval and the aT-eT/QT ratio for detecting coronary artery disease (CAD). The QT and aT-eT intervals were quantitated using computer-averaged QRS-T complexes and a computer program developed in our laboratory. Measurements were made on resting and exercise ECG recordings from a group of normal male subjects and a group of male pts. with angiographically documented CAD. The two groups were matched for age and heart rate. The QT interval measurements did not differ significantly between the two groups at rest. During exercise there were significant differences between the two groups in the aT-eT interval and the aT-eT/QT ratio.

	No. Pts.	aT-eT(msec)	QT(msec)	aT-eT/QT
NORMALS*	51	73.7	303.7	23.9
CAD PTS.*	29	60.6	305.4	18.9
		(p<0.01)		(p<0.001)

* Mean age 50; Mean Exercise H.R. 123/min.

The sensitivity and specificity of an aT-eT/QT ratio of <22% for underlying CAD was 82% and 70% respectively. The sensitivity of an aT-eT ratio of <22% and/or $\geq$1.0 mm. horizontal ST depression was 95%. We conclude that measurement of exercise QT interval changes is feasible using computer techniques and they show promise for inhancing the diagnostic capabilities of the exercise ECG.

PRECORDIAL ELECTROCARDIOGRAPHIC MAPPING IN THE IDENTIFICATION OF PATIENTS WITH LEFT MAIN STEM DISEASE.

John E. Deanfield, MB; Kim M. Fox, MB; Anne Jonathan; Andrew P. Selwyn, MB, Hammersmith Hospital, London, England.

The introduction of 16 lead precordial ECG mapping in exercise testing provides additional information not available using conventional lead systems. The value of this technique in identifying patients with left main stem (LMS) disease has been investigated in 50 patients. Over the same period, 90 patients with 3 vessel and 42 patients with single vessel disease were similarly investigated. The work load achieved was significantly lower in patients with LMS disease than the other two groups ($P<0.01$). Likewise the exercise-induced area and severity of ST-changes was greatest in patients with LMS narrowing ($P<0.01$). Discriminative function analysis showed that patients with LMS disease could be identified from the area and site of exercise-induced ST changes on the precordial map. Forty-four (88%) patients with LMS narrowing developed ST-changes on the uppermost row of the surface map; a finding, with 3 exceptions, that otherwise only occurred in patients with proximal left anterior descending coronary artery narrowing. This study therefore demonstrates the value of precordial exercise mapping in identifying patients with LMS disease.

THE SIGNIFICANCE OF BIPHASIC R WAVE AMPLITUDE CHANGES DURING INCREMENTAL ATRIAL PACING: A SENSITIVE AND SPECIFIC MARKER FOR ACUTE MYOCARDIAL ISCHEMIA

Daniel David, MD, James G. Kitchen, MD, FACC, Chin C. Chen, MD, Joel Morganroth, MD, FACC, Eric L. Michelson, MD, FACC, A.N. Moghadam, MD, FACC, Masahito Naito, MD, Leonard S. Dreifus, MD, FACC, Thomas Jefferson University and Lankenau Hospital, Philadelphia, PA

An increase in R wave amplitude (RWA) during exercise testing has been suggested as a marker for myocardial ischemia. This has been attributed to the "Brody effect" whereby ischemia results in an increase in LV volume. This study was designed to determine RWA response to myocardial ischemia induced by atrial pacing (AP). Twenty one patients (PTs) underwent AP during which the sum of RWA (ΣR) changes in leads X,Y,Z and V5 were correlated with the extent of angiographically determined CAD, resting LV end diastolic pressure (LVEDP) and ejection fraction (EF) as well as dynamic LV dimensional and functional changes during AP measured by 2D echocardiography in the short axis and apical view. Eleven of 13 (86.6%) PTs with negative AP showed a significant decrease in ΣR at 100/min ($p< 0.01$) followed by a further significant decrease in ΣR at 150/min ($p< 0.01$). In contrast, 7/8 (87.5%) PTs with positive AP demonstrated an initial significant decrease in ΣR at 100/min ($p< 0.01$) followed by a significant increase in ΣR at 150/min ($p < 0.01$). These patterns of ΣR changes during AP were not dependent on the degree of fixed CAD, the LVEDP or the EF either at rest or during AP. Thus, the distinctive pattern of an initial decrease followed by an increase in ΣR during incremental AP is a sensitive and specific marker for the occurrence of myocardial ischemia. This ischemic pattern is independent of both the degree of fixed coronary obstruction and left ventricular dimensional changes.

TUESDAY, MARCH 17, 1981
AM
CARDIAC SURGERY—2
10:30-12:00

THE IMMEDIATE POST-EXERCISE VENTRICULOGRAM: A SCINTIGRAPHIC TOOL FOR THE PRE-OPERATIVE ASSESSMENT OF REVERSIBLE MYOCARDIAL ASYNERGY

Alan Rozanski, MD; Daniel Berman, MD, FACC; Ronald Levy, MD; Richard Gray, MD, FACC; Marjorie Raymond, RN; Jamshid Maddahi, MD; James Forrester, MD, FACC; Alan Waxman, MD; H.J.C. Swan, MD, FACC; and Jack Matloff, MD, FACC.
Cedars-Sinai Medical Center, Los Angeles, California.

Since with upright exercise, normalization of resting LV asynergy (asyn) is frequently observed during the immediate post-exercise (IMPEX) period, the IMPEX response might be a useful pre-operative (op) indicator of latent mechanical myocardial function. Thus, we compared LV wall motion (WM) response IMPEX and following coronary artery bypass surgery (CABG) in 31 patients with coronary artery disease who underwent both pre-op 45° LAO multiple gated equilibrium scintigraphy (MGES) with sitting bicycle exercise and post-op resting MGES, using Tc-99m-RBCs. For each image, the LV was divided into 5 segments (segs) and WM assessed by a 5-point system (3=normal, -1=dyskinesis). Because of known effects of CABG on septal motion, this region was excluded from analysis. Pre-op asyn segs were considered improved IMPEX or post-op if WM=3 or increased $\geq$2 from control. Post-op and IMPEX images were separately compared to pre-op images. Of 35 pre-op asyn segs, the IMPEX response correctly predicted post-op WM in 27, including 16/23 segs which improved and 11/12 with no improvement ($p \leq 0.01$). Importantly, the IMPEX response was highly specific for reversible asyn: of 17 asyn segs improving IMPEX, 16 improved after CABG.

In conclusion: 1) post-operative improvement of resting asynergy occurs frequently, 2) the IMPEX response appears to differentiate segments with reversible and non-reversible asynergy, and 3) this response may thus be of clinical use in the pre-operative assessment of patients with resting left ventricular wall motion abnormalities.

RIGHT AND LEFT VENTRICULAR PERFORMANCE BEFORE AND AFTER CORRECTION OF MITRAL STENOSIS

Vincent C. DiCola, M.D., Charles A. Boucher, M.D., FACC, William H. Shea, Jr., B.S., Robert D. Okada, M.D., FACC, Frederick H. Levine, M.D., FACC, Demetrios Lappas, M.D. H. William Strauss, M.D., FACC, Gerald M. Pohost, M.D., FACC. Massachusetts General Hospital, Boston, MA.

The changes in RV and LV ejection fraction (EF) were assessed in relation to hemodynamics in 14 patients with isolated mitral stenosis (MS). RVEF was determined by both gated first pass (FP) and gated equilibrium (EQ) radionuclide methods and LVEF by EQ alone. Mean PA pressure (PAP), pulmonary vascular resistance (PVR), cardiac index (CI) and mean LA pressure (LAP) were recorded pre- and 1-2 days postoperativley. Mean $\pm$1 SD values follow:

	Preop	Postop	p
RVEF-FP	0.49$\pm$.13	0.60$\pm$.11	< .01
RVEF-EQ	0.35$\pm$.08	0.45$\pm$.09	< .001
LVEF-EQ	0.59$\pm$.10	0.58$\pm$.08	NS
PAP (mm Hg)	34$\pm$15	25$\pm$6	< .01
PVR (units)	5.2$\pm$2.5	3.2$\pm$1.8	< .001
CI (L/min/M^2)	2.4$\pm$0.4	2.7$\pm$0.4	< .05
LAP (mm Hg)	22$\pm$11	16$\pm$2	< .05

Preop FP RVEF correlated significantly with mitral valve area ($p<.05$). The increase in RVEF was larger in patients with lower preop RVEF ($r=-.62$, $p<.05$).
In conclusion, blood pool scanning permits further insight into the impact of mitral valve surgery on RV and LV function in MS. As assessed by 2 methods, RVEF is depressed preoperatively in relation to the severity of the MS and improves substantially postop. This improvement occurs in association with improved hemodynamics. LVEF is normal preop and does not change postoperatively.

OPERABILITY OF ADULTS WITH LEFT TO RIGHT SHUNTS, CYANOSIS, AND PULMONARY VASCULAR OBSTRUCTION

Verdi DiSesa, MD, William Grossman, MD, FACC, and Lawrence H. Cohn, MD, FACC, Harvard Medical School, Brigham and Womens Hospital, Boston, Massachusetts 02115

Patients with left-to-right shunts who develop desaturation, severe pulmonary artery hypertension (PAH), and marked functional disability have been considered inoperable or at very high risk for ablation of the shunt.

Four patients (22-45, 32 years) with an atrial septal defect, ventricular septal defect, patent ductus arteriosus and Pott's shunt with Tetralogy, respectively presented with functional class IV symptoms, mild cyanosis (mean arterial saturation = 90% (88-92)), PAH ($\overline{PA}$ of 50-83, 66), R_p/R_S of 0.29-0.43, 0.36, and while right-to-left shunt was present in all patients, the net Q_p/Q_S was 1.3-2.8, 1.9. PA pressure did not fall in 3/4 breathing 100% O_2 and two had class IV-V pulmonary hypertensive lung changes on biopsy.

All survived operation, became acyanotic and are functional class I-II, 15-72 months postoperatively. All were recatheterized 4-18 months postoperatively: defects were closed, the $\overline{PA}$ pressures were 26-45, 35 and R_p/R_S were 0.16-0.60, 0.39.

Patients with left-to-right shunts who develop cyanosis and severe pulmonary vascular obstruction may still be candidates for surgical correction if Q_p/Q_S is net left-to-right and if R_p/R_S is less than 0.50.

MYOMECTOMY AND MITRAL VALVE REPLACEMENT FOR IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS: FIVE YEAR FOLLOW-UP.

Robert D. Leachman, MD, FACC, Zvonimir Krajcer, MD, FACC, Denton A. Cooley, MD, FACC, Texas Heart Institute, Houston, Texas.

To assess the long term results of myomectomy (MYOM), mitral valve replacement (MVR) or combination of both in 36 patients (pts) with idiopathic hypertrophic subaortic stenosis (IHSS) pre- and postoperative cardiac catheterization, functional classification (FC) and mortality were analyzed. The follow-up was from 5 to 67 months (mean 48). Hemodynamic measurements included LV outflow tract gradient (LVOTG) at rest and with provocation and LV end-diastolic pressure (LVEDP) in mmHg. There was no operative mortality. There were three late post-operative deaths. Two had MVR and one had MYOM. They all had preoperatively severe congestive heart failure (CHF), FC IV and LVEDP > 20 mmHg.

	Preop (36)	MVR (13)	Postop MYOM (12)	MVR$\pm$MYOM (11)
FC	35 III & IV	10 I & II	12 I & II	11 I & II
LVOTG REST	72 $\pm$42	3 $\pm$ 6***	35 $\pm$15**	0****
LVOTG PROV	143 $\pm$56	4 $\pm$ 9****	78 $\pm$21***	0****
LVEDP	22 $\pm$11	14 $\pm$ 5*	19 $\pm$14	16 $\pm$7

*=p <0.05; **=p <0.02; ***=p < 0.01; ****=p <0.001

Our findings indicate that surgery for IHSS carries a low operative risk, offers marked symptomatic improvement and produces significant reduction in LVOTG and LVEDP. MVR or MVR plus MYOM was more effective than MYOM alone in reducing resting and provocative LVOTG and LVEDP. Pts with severe CHF, FC IV and significantly elevated LVEDP have less favorable long term post-operative prognosis.

OPEN MITRAL COMMISSUROTOMY: LATE FOLLOW-UP OF 108 PATIENTS

Daniel J. Ullyot, M.D, FACC; Benson B. Roe, M.D, FACC; Noel Fishman, M.D; John Mack, M.D; Kevin Turley, M.D, FACC; Paul A. Ebert, M.D, FACC, University of California, San Francisco, California.

During the period January 1965 through July 1979 145 patients were operated on for isolated mitral stenosis. 128 had an open operative approach and only 13% (17/128) required mitral valve replacement. 111 patients underwent open mitral commissurotomy with a hospital survival of 97% (108/111).

These 108 patients were followed a mean of 6.5 years (range 1-15). There were 101 women and 7 men, mean age 46 years (range 23-67), NYHA classification I (1%) II (30%) III (64%) IV (5%), mean valve area .94 square centimeters (range 0.4-1.8).

There were 7 late deaths, one due to cardiac and 6 of either non cardiac (3) or unknown (3) cause. Twenty required subsequent mitral valve surgery either mitral valve replacement (18) or a second open commissurotomy (2). Seven had systemic thromboembolic events. Seventy eight percent were in NYHA class I or II at recent follow-up. Life table analysis showed:

	Cumulative % (S.E.)		
	5 yr.	10 yr.	15 yr.
Survival	97 (1.9)	92 (2.6)	89 (3.5)
Reoperation-free	92 (2.9)	83 (4.2)	75 (5.2)
Embolus-free	99 (1.0)	94 (2.5)	89 (3.6)

Results demonstrate that when open mitral commissurotomy is possible, excellent symptomatic improvement, prolongued survival, and a low incidence of reoperation and/or embolization can be expected.

REPAIR OF RHEUMATIC AORTIC REGURGITATION IN ADOLESCENCE

George E. Reed, M.D., FACC, Richard A. Moggio, M.D., Richard W. Pooley, M.D., Eugenie F. Doyle, M.D., FACC, Brian Kiely, M.D., and Monika Rutkowski, M.D., Dept. of Surgery, N.Y. Medical College, Valhalla, N.Y.

The management of severe rheumatic aortic regurgitation in young people continues to be difficult. The reported early failure as a result of calcification of porcine prostheses in young patients suggests that aortic prostheses and the need for continuous anticoagulation remain serious problems in this group.

A concept of repair is presented in which three dimensional anatomy is restored by creating fuller cusps. This permits apposition both horizontally and vertically over a wide area. The technique involves insertion of a "T" shaped gusset of antologous tissue which has been formed by measurement and which allows for shrinkage.

Five children have been operated upon and have been followed for from 18 months to 13 years. Three of the five patients had mitral repair in addition to aortic valvuloplasty. One patient was reoperated four years later; both mitral and aortic valve required replacement. Sustained good results in the others have been documented clinically and by repeat cardiac catheterization in three.

At minimum this operation permits growth of the aortic root so that a suitably large prosthesis can ultimately be inserted if necessary.

TUESDAY, MARCH 17, 1981
AM
VALVULAR HEART DISEASE
10:30-12:00

HAS ECHOCARDIOGRAPHY ANY PLACE IN DETERMINING THE TIMING OF OPERATION IN AORTIC REGURGITATION?

Martin St. John Sutton, MD, Nathaniel Reichek, MD, John Hirshfeld MD, John Kastor MD, FACC, University of Pennsylvania, Philadelphia, PA.

In chronic aortic regurgitation(AR) valve replacement is advised in patients(pts), 1) with symptoms, and, 2) with LV end-systolic echo diameter $\geq$5.5 cm. To reassess the value of echocardiography in the management of pts with AR we compared the preop LV echoes from 20 symptomatic (NYHA class 3 or 4) pts (group 1) who underwent surgery, with 23 asymptomatic pts (group 2) treated medically, (for a mean of 2 years), to determine whether these 2 groups could be distinguished. All pts were catheterized and had severe AR and normal coronary arteries. LV echograms were digitized and analyzed by computer so that measurements could be made of LV diameter(D) and wall thickness(W) at end-systolic(s) and end-diastole(d), peak rates of LV shortening(VCF), LV filling, dD/DT, and wall thickening, +dW/dt, and wall thinning, -dW/dt.

	Ds	Dd	Wd	VCF	dD/dt	+dW/dt	-dW/dt
Group 1	4.7	7.0	1.1	2.2	16.5	3.7	8.6
	$\pm$0.6	$\pm$0.6	$\pm$0.1	$\pm$0.4	$\pm$4.5	$\pm$0.8	$\pm$2.0
Group 2	5.1	7.0	1.2	1.9	14.5	3.3	5.8
	$\pm$0.9	$\pm$0.6	$\pm$0.3	$\pm$0.5	$\pm$4.0	$\pm$1.0	$\pm$2.2

Eight pts had LVDs >5.5 cm 5 in group 1 and 3 in group 2, but there were no significant differences between the two groups in, 1) LV size, 2) LV hypertrophy(Wd), 3) peak VCF 4) peak LV filling rate, 5) peak rate of wall thickening or thinning. Since echo could not distinguish surgically treated (group 1) pts from medically treated pts (group 2) in terms of LV function, we conclude that no single or combination of echo measurements should be used to recommend operation in pts with chronic AR.

NONINFLAMMATORY AORTIC ROOT DISEASE: AN IMPORTANT CAUSE OF AORTIC REGURGITATION. ECHOCARDIOGRAPHIC AND HISTOPATHOLOGIC CORRELATION.

Timothy Guiney, MD, Graham Leech, MA, Michael J. Davies, FRCPath., Alan Wilson, FRCR, John Parker, FRCS, and Aubrey Leatham, FRCP. St. George's Hospital and Medical School, London, England.

Seventy-one consecutive patients undergoing aortic valve replacement for isolated aortic regurgitation (AR) in a 4 year period were assessed with preoperative M-mode measurement of aortic root diameter (ARD) and the results compared with gross and histologic examination both of the cusps removed and of aortic wall biopsies taken at surgery. Of those patients with ARD $<$37mm 40/42 (95%) had normal aortic wall histology but disease of the aortic cusps (rheumatic, endocarditis, etc.) causing the AR. Of those with ARD $\geq$ 37mm 24/29 (83%) had normal cusps but aortic wall disease accounting for the AR. Only 6 of these patients had inflammatory root disease (lues, giant cell arteritis, Reiter's, etc.). The remainder demonstrated patchy disruption of smooth muscle and particularly of elastic laminae without inflammatory cell infiltration. Twenty of the entire series of 71 patients (28%) proved to have noninflammatory aortic root disease, leading to aortic root dilatation and aortic regurgitation on that basis. Noninflammatory aortic root disease, the most common cause of severe AR in this group, was noted more frequently in those of British ancestry than in minority or immigrant group patients in whom rheumatic etiology was more prevalent. The progression of symptoms was more rapid than in the rheumatic group, but slower than in those with endocarditis.

This group of patients, with a common but poorly recognized cause of severe AR, can be readily identified noninvasively and may require closer pre-symptomatic follow up than those with more slowly progressing types of AR.

EFFECT OF PROLONGED PRAZOSIN TREATMENT ON THE HEMODYNAMICS AND CARDIAC ELECTROLYTES AND Na^+-K^+-ATPase IN DOGS WITH CHRONIC AORTIC STENOSIS

Cathey L. O'Neil, BSc; Bakunth Bharadwaj, MD, FACC, Kailash Prasad, MD, Ph.D, FACC, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

It has been shown that there is a decrease in the cardiac function and intracellular calcium and an increase in the cardiac ATPase in dogs with chronic aortic stenosis. Prazosin, has been used in the treatment of congestive heart failure. It is, however, not known whether Prazosin gives only haemodynamic benefit with accompanying subjective improvement or if there is an actual improvement in the condition of the myocardium in terms of electromechanical and biochemical changes. The present investigation therefore, deals with the effect of prolonged treatment with Prazosin on the cardiac function, electrolytes, and ATPase in dogs with chronic aortic stenosis. Aortic banding was performed in 18 dogs after chest X-ray, ECG and haemodynamic parameters were assessed. Two groups each of 6 dogs were sacrificed at 3 and 6 months after aortic banding. Another group of 6 dogs was treated with Prazosin for 3 months after 3 months of aortic banding and then sacrificed. There was a significant decrease in the cardiac function and contractility associated with an increase in the cardiac ATPase and a decrease in the intracellular calcium at 3 and 6 months of aortic banding and that was more so at 6 than at 3 months. Prazosin produced a marked improvement in the myocardial function, a decrease in the ATPase and an increase in the intracellular calcium. These results indicate that Prazosin not only tended to reverse the cardiac function and contractility to control levels but also tended to reverse the ATPase and intracellular Ca^{++} towards control levels.

AORTIC INPUT IMPEDANCE IN MITRAL REGURGITATION

Wilmer W. Nichols, PhD, FACC; Carl J. Pepine, MD, FACC; Jawahar Mehta, MD, FACC; Leonard G. Christie, JR., MD, FACC; C. Richard Conti, MD, FACC, University of Florida, Gainesville, Florida

To define the effects of mitral regurgitation (MR) on the systemic vascular system pulsatile pressure-flow analysis was performed in 19 patients. The aortic input impedance spectrum was determined from recordings of high fidelity pressure and flow waves (multisensor catheter) obtained from the ascending aorta. Eight patients had clinical and hemodynamic evidence of 3+ to 4+ MR. The other eleven patients had no evidence of heart failure or valvular heart disease and were used as a control group. In the MR patients, both input resistance (impedance at zero Hz) and characteristic impedance (mean of impedance moduli > 2Hz) were significantly elevated (2202 $\pm$ 206 vs. 1080 $\pm$ 49 dyne-sec-cm^{-5} and 123 $\pm$ 7.5 vs. 73 $\pm$ 9 dyne-sec-cm^{-5} respectively; both $p < .001$) compared to age and arterial pressure matched control subjects. Oscillations of impedance moduli, represented by the difference between maximum and minimum moduli were also significantly increased (101 $\pm$ 3.8 vs. 56 $\pm$ 6.1 dyne-sec-cm^{-5}; $p < .001$) in the MR patients compared to the control subjects. The increased aortic input resistance and characteristic impedance in the MR patients suggests peripheral vasoconstriction and increased aortic stiffness. The larger oscillations in the impedance moduli indicate an increase in pressure and flow wave reflections. These pressure-flow alterations reflect changes in aortic distensibility and arteriolar cross-sectional area resulting in an increased vascular load on the left ventricular in patients with MR.

IDIOPATHIC PROLAPSE OF THE MITRAL VALVE: FOLLOW-UP STUDY OF 136 PATIENTS STUDIED BY ANGIOGRAPHY

Jorge Belardi, MD; Hector Lardani, MD; William Sheldon, MD, FACC; Cleveland Clinic Foundation, Cleveland, Ohio

One hundred thirty-six patients (pts) with angiographically proven prolapse of the mitral valve were followed for 6-15 yrs, mean 9.9 yrs (100% follow-up). Pts with rheumatic or atherosclerotic heart disease were excluded. Mean age was 47, range 9-75 yrs. Ninety-two pts (67.6%) were alive without serious complications, most of them with normal ECGs and competent mitral valve. Six pts (4.45%) died suddenly (age 22-69) all with abnormal ECGs, variable degree of prolapse and only 1 with significant mitral regurgitation (MR). Two pts died with progressive cardiac failure. Mitral valve replacement was performed in 16 pts for severe MR: ruptured chordae was found in 9 pts and endocarditis in 3; 2 pts died within 30 days and 2 later on after surgery. Other nonfatal complications were: endocarditis in 5 pts (3.6%); stroke 6 pts (4.4%); AV block 4 pts (2.9%); recurrent ventricular arrhythmias 5 pts (3.6%); atrial fibrillation 14 pts (10.2%); compensated congestive heart failure 1 pt. These complications occurred in a total of 39 pts (28.9%) in which there was a high incidence of late or pansystolic murmurs instead of isolated clicks, they also had abnormal ECGs and significant MR. The degree of prolapse was similar in the complicated and uncomplicated groups. The majority of pts had a favorable prognosis (67%). However, a significant number of complications occurred with long-term follow-up. Normal ECG, isolated midsystolic clicks and competent mitral valve carries a good prognosis. MR is associated with a high incidence of fatal and nonfatal complications. The degree of prolapse does not have predictive value.

THE EFFECT OF ACUTE AORTIC INSUFFICIENCY ON THE DYNAMICS OF MITRAL VALVE MOTION AND INSTANTANEOUS TRANS-MITRAL FLOW: HEMODYNAMIC MECHANISM FOR THE AUSTIN FLINT MURMUR

Shlomo Laniado, MD, FACC; Edward L. Yellin, PhD; Chaim Yoran, MD, FACC: Joel Strom, MD; Masatsugu Hori, MD; Shlomo Gabbay, MD; Robert W. M. Frater, MD, FACC; Albert Einstein College of Medicine, New York, N.Y.

Acute reversible aortic insufficiency (AI) was induced in 31 experiments in open-chest anesthetized dogs with a basket-tipped catheter introduced through the aortic valve. Controlled regurgitation ranged from 30-70%. Instantaneous trans-mitral flow was registered by a supra annular electromagnetic flow probe. In addition aortic flow, LV, Ao, and LA pressures, and intra cardiac phonocardiogram were recorded. Simultaneously with the hemodynamic measurements, M-mode and 2-D mitral valve echograms were recorded before, during and after AI. With creation of AI, mitral stroke volume decreased immediately 25% (from control of 25$\pm$0.6ml (mean$\pm$S.E.M.) to 18$\pm$0.7ml), but within few beats reached a steady state of 84% of control (21$\pm$0.5ml) ($P<0.001$). Mid-diastolic peak mitral flow velocity (PMFV) dropped instantly to 87% of control ($P<0.01$) however after few beats, during steady state, it increased to surpass control level by 10% ($P<0.05$). Mitral valve echograms revealed that during AI there was a constant decrease (8-15%) in the amplitude of cusp opening. All hemodynamic and echographic changes returned to control levels with the cessation of AI. It is concluded that 1) the increase in PMFV serves to partially compensate for the reduction of total stroke filling volume (and cardiac output) in AI, 2) the increase in PMFV in the presence of reduced valve opening provides a logical hemodynamic explanation for the mechanism of Austin Flint murmur.

TUESDAY, MARCH 17, 1981
AM
LEFT VENTRICULAR MECHANICS IN CHRONIC VALVULAR DISEASE AND TREATMENT OF REFRACTORY LEFT VENTRICULAR FAILURE
10:30-12:00

LEFT VENTRICULAR FUNCTION AND STIFFNESS BEFORE AND AFTER SUCCESSFUL SURGERY FOR MITRAL REGURGITATION.

Florent de Vernejoul, MD ; Françoise Herreman, MD ; Claude Boffety, MD ; Charles Cosma, MD ; François Guerin, MD ; Michel Degeorges, MD. Cochin Hospital, U.E.R. Paris, France.

Left ventricular function (LVF) and stiffness were assessed by hemodynamic and cineangiographic study in 33 patients with chronic mitral regurgitation (MR) before and 14 ± 9 months following valve correction. After surgery, pulmonary and LV end-diastolic pressures decreased ($P < 0.001$), cardiac index increased ($P < 0.01$). LV mass (LVM), end-diastolic volume (EDV), end-systolic volume and stroke volume decreased ($P < 0.001$). LV shape, more spherical before surgery, reverted to normal. Ejection fraction (EF) decreased with no change of mean velocity of circumferential fiber shortening ($\overline{VCF}$). Chamber stiffness reverted to normal ($P < 0.01$), LV myocardidal elasticity (Em) and stiffness constant (K) decreased ($P < 0.01$).

	LVM g/m2	EDV cm3/m2	EF %	$\overline{VCF}$ circ./s	Em g/cm2	K
Pre	141±52	153±42	55±15	1.1±.3	633±279	17.9±1.6
Post	102±39	94±28	49±14	1.0±.3	372±235	16.7±1.9
P	<0.001	<0.001	<0.05	NS	<0.01	<0.01

Surgical correction of MR determined regression of LV dilatation-hypertrophy with normalisation of shape and incomplete improvement of myocardial stiffness. These changes were not associated with improvement of LVF. In conclusion these findings suggest that myocardial alterations fail to regress in spite of successful repair of MR.

SYSTOLIC MECHANICS DURING SURGICAL CORRECTION OF CHRONIC MITRAL REGURGITATION

Calvin Y.H. Wong, MD; Henry M. Spotnitz, MD, FACC; Columbia University College of Physicians and Surgeons, New York, N.Y.

M-mode and 2-D echocardiography were combined with LV pressure-flow data to analyze systolic mechanics during valve replacement for chronic mitral regurgitation (CMR) using a changing volume spherical model. Preop RAO angiography provided LV mass and a regression correlating M-mode diameter with LVEDV (r=.82). Flow-velocity data was calibrated by thermal dilution.

Both M-mode (n=6) and 2-D (n=6) echo reveal large decreases in early postoperative shortening fraction (SF) (-24±17(SD)% p<.01 M-mode, -20±18% p<.03 2-D) which are significantly different from small changes in control populations (+7±10% n=25 M-mode, -1±14% n=22 2-D). In 5 CMR patients, the integral of LV wall stress increases significantly after valve replacement (26±6 g/cm sq. preop vs. 36±7 postop, p<.02), which may produce decreased SF. Compared with 5 patients undergoing coronary revascularization. LVEDV (437±213 vs. 128±33 ml) and mass (521±190 vs. 195±42 g) are increased in CMR (p<.02). Peak fiber shortening velocity (.21±.08 vs. .48±18 circ/sec, p<.02) and SF are decreased. But 14 additional hemodynamic and structural parameters are not significantly different. These results emphasize the derangement of preoperative LV function in CMR and highlight deterioration of volume-related vs. pressure-related parameters of LV performance.

NONINVASIVE DETERMINATION OF THE ENDSYSTOLIC PRESSURE VOLUME RELATION IN PATIENTS WITH AORTIC REGURGITATION

Gerhard Schuler, Klaus v. Olshausen, Helmut Mehmel, Franz Schwarz, HJ Hermann, Wolfgang Kübler, FACC Medizinische Universitätsklinik, Heidelberg, Germany

Previous reports indicated that the left ventricular endsystolic pressure volume relation (ESPV) is a sensitive parameter of myocardial contractility independent of preload and afterload. In order to determine LV-ESPV noninvasively we measured changes in endsystolic volume by gated radionuclide angiography (RNA) in 14 patients (pt) with chronic aortic regurgitation and in 9 normals. Peak systolic pressure was measured by automated cuff and substituted for endsystolic pressure. Variations in blood pressure were achieved by i.v.methoxamine, while heart rate was kept within narrow limits by atropine. In order to detect stress induced LV dysfunction both groups also underwent maximal graded bicycle exercise (EX) while changes in LV ejection fraction were determined by RNA. In normals the slope k of the ESPV ranged from 4 to 8 and LV ejection fraction (EF) rose by more than 5% during EX. In pts with aortic regurgitation two subgroups could be identified. GROUP A (n=8): there was marked depression of k ($k < 3$) despite a normal resting EF; these pts also developed LV-dysfunction during EX (rise in LV-EF < 5%). GROUP B (n=6): the slope k fell within the normal range (n=4) or was only marginally depressed ($4 > k > 3$; n=2); LV reserve proved to be normal in these pts (rise in LV-EF > 5%). All pts were NYHA class I or II. We conclude: the slope of the ESPV is readily determined by RNA and cuff pressure measurements; it is highly sensitive to early impairment of myocardial contractility and correlates well with stress induced LV dysfunction in pts with aortic regurgitation whose resting ejection fraction is still within the normal range.

POTENTIAL VALUE OF ORAL β_2 ADRENOCEPTOR AGONISTS IN LEFT VENTRICULAR FAILURE.

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This study was designed to assess the haemodynamic effects and metabolic consequences of β_2 adrenoceptor agonists in left ventricular failure. IO patients with severe left ventricular dysfunction secondary to coronary artery disease received an oral dose of pirbuterol 20mg or salbutamol 6mg and haemodynamic and metabolic effects were measured 30, 60 and 90 minutes later.

After 30 minutes systemic vascular resistance fell. from 23 to 19 units ($p<0.01$) and cardiac output increased from 3.7 to 4.5 L/min ($p<0.01$) although mean arterial blood pressure remained unchanged. Left ventricular dp/dt max increased from 921 to 1411 mmHg/sec despite a fall in pulmonary artery diastolic pressure from 19 to 17 mmHg ($p<0.05$). Myocardial blood flow (152 to 162 ml/min) and oxygen uptake (15.2 to 15.0 ml/min) did not change significantly. Myocardial extraction of lactate, glucose and free fatty acids remained unchanged. These effects were maintained for 90 minutes and we observed no important differences in the responses to pirbuterol or salbutamol.

These results indicate that in patients with left ventricular failure β_2 adrenoceptor agonists improve myocardial performance by a combination of afterload reduction and positive ionotropism, and this effect is achieved at little net metabolic cost to the ischaemic myocardium.

HEMODYNAMIC EFFECTS OF A NEW BETA$_1$-AGONIST (PRENALTEROL) IN PATIENTS WITH CONGESTIVE HEART FAILURE

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Beta$_1$-stimulation is a new therapeutic approach in severe congestive heart failure. The hemodynamic effects of a new beta$_1$-agonist - prenalterol (P) - were analysed in Patients with chronic heart failure due to coronary artery disease (n = 6) and congestive cardiomyopathy (n = 6). All patients were only on digitalis and diuretica and were in class III - IV NYHA. Left ventricular systolic and end-diastolic pressure (LVSP, LVEDP) were obtained with micro manometer before (C) and 20 min after infusion of 12 mg P. Peak (+) and (−) dp/dt as well as the time constant (T) of isovolumic exponential pressure decline were determined. Cardiac index (CJ) was received by thermodilution techniques, LV volumes and ejection fraction (EF) by cineangiocardiography. All values (± sem) were determined at a constant heart rate of 100 beats/min before and after P by atrial stimulation. LVSP remained constant

	LVEDP mm Hg	+dp/dt mm Hg/sec	-dp/dt mm Hg/sec	T msec	CJ l/min x m^2	EF %
C	21,4 ± 3,4	1164 ±111	1057 ± 85	62,4 ±4,9	3,6 ± 0,3	24 ± 3
P	14,9 ± 3,2	1587 ± 190	1268 ±118	44,5 ±5,9	4,2 ±0,4	30 ±4
p	< 0,001	< 0,005	< 0,005	< 0,005	< 0,002	< 0,002

Simultaneous analysis of pressure and volume revealed, that LV power increased from 6,5 ± 0,8 to 7,8 ± 0,9 W ($p < 0,02$) and LV work from 1042 ±129 to 1200 ± 145 Wsec ($p < 0,02$). LV wall stress remained constant 32,6 ± 3,0 and 29,4 ±2,2 kPa. Diastolic pressure-volume analysis showed that LV ventricular compliance decreased from 22,1 ±4,7 to 13,4 ± 1,7 x 10^{-3} ml^{-1} and myocardial compliance from 70,8 ± 14,2 to 47,2 ± 5,1 x 10^{-3} cm^{-1}.

We conclude, that prenalterol increased LV contractility and relaxation, improved LV ejection and LV compliance, characteristic phenomena of beta$_1$-agonists. LV function curve was shifted to the left and upwards. The improvement of LV function underlines that beta$_1$-stimulation is a promising new approach for treatment of severe congestive heart failure.

LONG TERM EFFECT OF ORAL AMRINONE IN HEART FAILURE: IMPROVEMENT IN EXERCISE PERFORMANCE DESPITE DECLINING LEFT VENTRICULAR PUMP FUNCTION

Lewis Siegel, MD; Joel Strom, MD; Eugene Fein, MD; John Wexler, MD; Carol Maskin, MD; Thierry LeJemtel, MD; Edmund Sonnenblick, MD, FACC, Albert Einstein College of Medicine, Bronx, New York.

Thirteen patients (pts) with severe congestive heart failure (NYHA Class IV), demonstrating initial hemodynamic improvement with Amrinone therapy, were serially evaluated with M-mode echocardiography (ECHO), multigated radionuclide ejection fraction (EF), and Naughton protocol treadmill exercise testing, to evaluate the chronic effects of Amrinone on LV performance, and functional capacity. Pts were observed for an average follow-up period of 8 months (mos), range (3-17 mos). Baseline studies revealed a mean ECHO LV end diastolic diameter (EDD) of 7.2±0.2 cm, EF 14±1.4%, and exercise capacity of 4.4±1.0 minutes (min). Within 3 mos, a sustained improvement in exercise capacity 6.6±2.2 min, was demonstrated despite a progressive increase in LVEDD, 7.5±0.3 cm. During a late follow-up period (3 to 17 mos), there was a further increase in LVEDD, 7.8±0.3 cm, however, functional capacity continued to improve, 11.4±1.3 min. EF at 3 mos, and > 3 mos. were 18.3±2% and 12±2.8%, and not significantly different. The data suggests that with Amrinone therapy, there is an initial and sustained improvement in functional capacity despite the progression of underlying LV disease, evidenced by the increasing LVEDD. A persistent inotropic effect may explain the maintenance of an improved stroke volume and net LV performance.

TUESDAY, MARCH 17, 1981
AM
THE ATRIO-VENTRICULAR NODE
10:30-12:00

AUTONOMIC MODULATION OF A-V NODAL CONDUCTION IN CONSCIOUS DOGS.

John X. Thomas, Jr., Ph.D. and Walter C. Randall, Ph.D., FACC, Loyola University Medical Center, Maywood, Illinois

The autonomic nervous system can exert considerable influence on the conduction properties of the A-V node. The purpose of these experiments was to evaluate the role of this innervation under conditions when autonomic tone is minimal. The maximal atrial pacing rate with 1:1 A-V conduction (Rmax) was determined in 10 unanesthetized dogs which had been previously instrumented with 2 bipolar right atrial electrodes. Each dog was paced from 80-400 beats/min in a random sequence while recording a Lead II EKG. Resting heart rate of all dogs was 95±2. Rmax under control conditions was 131±6. After propranolol (Prp, 1.0 mg/kg, IV) Rmax was reduced to 118±11 ($p=.022$). After atropine (A, 0.2 mg/kg, IV) Rmax was increased to 344±10 ($p<.001$). After both A and Prp Rmax was 316±10 (different, $p<.05$, from A group). Rmax was also determined in 6 additional dogs which had previously undergone a surgical denervation of the A-V nodal region and ventricles. Rmax was 293±7 (not different, $p=0.21$, from Rmax in control dogs after A and Prp). In another group of dogs (n=3), heart rates were monitored for 24 hrs via a Holter monitor. After the resting heart rate was determined (81±3) each dog was paced at 10 beats higher than its resting rate via a Medtronics demand pacemaker. During the 24 hr period there were bouts of A-V block, which were not abolished by concommittant treatment with P. These data indicate that in conscious dogs with surgically denervated or pharmacologically blocked A-V nodes, impulses can be conducted at very rapid rates. Blockade of the sympathetics in neurally intact dogs with Prp reduced Rmax slightly, however the effects of parasympathetic blockade were much more prominent. Resting tone is predominantly parasympathetic.

CLOSED CHEST PERMANENT ATRIOVENTRICULAR BLOCK IN DOGS: TECHNIQUE AND ANATOMIC CHANGES

R. Gonzalez, MD; M. Scheinman, MD, FACC; W. Margaretten, MD; S. Bharati, MD; M. Lev, MD, FACC; University of California, San Francisco, Ca.

Complete atrioventricular block (AVB) was produced in 9 consecutive dogs using a direct current (D/C) defibrillator and an electrode catheter in which 2/3 of the electrode surface was insulated. The catheter was inserted by vein and positioned to record the His bundle deflection. D/C shocks of 140 joules were delivered from the catheter electrode to a plate behind the back. Complete AVB was induced with one shock in 6 dogs and with 2-4 shocks in 3. Complete AVB persisted for 3 months prior to sacrifice. The QRS duration was prolonged (≥120 msec) and a His bundle potential could not be recorded from either right or left heart electrode catheters. The mean spontaneous ventricular cycle length (1575±350 msec) decreased after exercise (1230±217) ($p<0.01$), increased after intravenous (0.2 mg/kg) propranolol (1710±409) ($p<0.05$), but did not change after intravenous (0.04 mg/kg) atropine. The change in rate after exercise was abolished by propranolol. No gross myocardial or valvular damage was present and histologic studies of the AV conduction system were completed in 5 dogs. In dogs receiving a single shock, less severe degenerative, fibrotic and necrotic changes were observed in the AV node, its approaches and in the penetrating and branching portions of the His bundle than when multiple shocks were required. We describe a simple technique for production of chronic AVB, the emerging pacemaker is fascicular or ventricular and modulated by changes in sympathetic tone. The absence of valvular or myocardial damage provides an excellent animal model for physiologic experiments and may be of value in patients with drug resistant supraventricular tachycardia.

MEMBRANE CURRENT SYSTEMS IN THE RABBIT ATRIOVENTRICULAR NODE. THE FIRST VOLTAGE CLAMP STUDY

Masao Nishimura, MD; Shinichiro Kokubun, MD; Akinori Noma, MD; Hiroshi Irisawa, MD; Yoshio Watanabe, MD, FACC, Cardiovascular Institute, Fujita Gakuen University, Toyoake, Aichi, Japan

To investigate the membrane current systems in the rabbit atrioventricular node (AVN), small preparations with final dimensions of 0.2 x 0.2 x 0.2mm were dissected from the middle portion of AVN. These preparations generally showed spontaneous action potentials with configurations quite similar to those of N cells. Voltage clamp was conducted with double microelectrode techniques as used by Noma and Irisawa on sinoatrial node (SAN). During voltage clamp, the membrane potential was usually held at -40mV, where the steady net current was about 0. A transient inward current (TIC) was recorded on depolarization between -40 and +35mV, becoming maximal at around -10mV. The TIC reached its peak 5-10ms after the onset of the test pulse, and was inactivated with a time constant of 15-30ms. This current was identified as the slow inward current since it was insensitive to tetrodotoxin and abolished by D-600. The depolarization-induced TIC was followed by a slow increase in the outward current, which, on clamping back to the holding potential, showed a gradual decay with a time constant of 189 ± 24ms (n=6). The reversal potential, obtained at 10 and 20mM K^+ Tyrode, decreased with a slope of 61mV for a 10-fold increase in $[K]_o$ (n=4), indicating this outward current to be carried by K^+. On hyperpolarization from -40 to -70 and -80mV, a large inward current was observed with a time constant of 3s. These findings suggest that AVN possesses membrane current systems quite similar to those in SAN, and that a common ionic mechanism underlies automaticity and slow conduction in these two nodal structures in the heart.

ADDITIONAL EVIDENCE FOR ADENOSINE MEDIATION OF A-V CONDUCTION DISTURBANCES IN CANINE MYOCARDIUM.

Luiz Belardinelli, MD; Elizabeth Mattos, MD; Fernando A. Lucchese, MD; Robert M. Berne, MD. Instituto de Cardiologia RS, Porto Alegre, Brasil, Dept. of Physiol., Univ. of Virginia, Charlottesville, VA.

We reported that the A-V conduction delay caused by adenosine (Ado) or hypoxia is markedly attenuated by 10^{-5}M Aminophylline (Am), an Ado competitive antagonist. In additional studies on 22 anesthetized dogs A-V conduction time (AVCT) and AH and HV intervals, His-bundle, atrial and ventricular surface electrograms were recorded. The A-V node artery (AVNA) was cannulated for selective infusion of drugs into the A-V node region. In 16 of the dogs, Ado (as a 1 ml-bolus of 10-1000µg) transiently increased the AVCT due solely to a lengthening of the AH interval. Ado at 10µg and 100µg dose prolonged the AH interval from a control value of 55±5msec to 80±5msec and 105±10msec, respectively. At 1000µg, Ado produced 2nd degree A-V block. Duration of the transient increase of AVCT was also dose-dependent. Pretreatment with dipyridamole (250µg/kg), an inhibitor of Ado uptake, potentiated the effects of Ado in magnitude and duration, whereas Am attenuated the effects of Ado. In 6 dogs, within 10 min after AVNA cannulation, the AH (but not HV) interval was prolonged, and, 2nd degree A-V block occurred. Injection of Am (5 mg/kg IV) or of theophylline (100 or 1000µg) into the AVNA rapidly reversed the A-V block. Upon washout of the drugs the A-V block reappeared. Thus, if the blood supply to the A-V node is sufficiently impaired by AVNA occlusion release of endogenous Ado could explain the observed A-V block; reversal of the block by methyl xanthines supports this suggestion. We conclude that endogenously released Ado may account for a major fraction of the acute A-V conduction disturbance associated with myocardial ischemia.

ELECTROPHYSIOLOGICAL MECHANISMS OF AV CONDUCTION IN RESPONSE TO ATRIAL FIBRILLATION REVEALED BY MULTIPLE SIMULTANEOUS EXTRACELLULAR AND INTRACELLULAR RECORDINGS

Todor Mazgalev, PhD, Leonard S. Dreifus, MD, FACC, John Bianchi, Eric L. Michelson, MD, FACC, Thomas Jefferson University and Lankenau Hospital, Philadelphia, PA

Atrial fibrillation (AF) was induced in 20 superfused rabbit atrial-AV nodal (AVN) preparations in which simultaneous extracellular bipolar electrograms were recorded from the crista terminalis (CT), interatrial septum (IAS) and His bundle (H) along with microelectrode action potential recordings from cells in the AN, N and NH regions to map AVN activation. Effective engagement of the AVN with optimal propagation to the N region was critically dependent on both the timing and interaction of the random inputs arriving from the CT and IAS regions; whereas cancellation and fractionation of the random inputs resulted in concealed and manifest block. Conduction through the AN and N region was also influenced by the degree of inhomogeneous activation of fibers forming the predominant conduction pathway. Fragmentation of the wavefront of upstream fibers was responsible for multiple graded responses in the N region rather than electrotonic spread or reentry mechanisms. Engagement of the NH region always produced a 1:1 NH to H relationship. Conclusions: 1) Activation of the AN region occurs randomly via inputs from both the CT and/or IAS in AF; 2) Effective engagement of the AN and N regions is both time and voltage dependent so that downstream propagation is critically related to the degree of synchronous activation of both AN and consequently N fibers; 3) Fractionation and cancellation of wavefronts rather than reentry mechanisms within the AVN can account for decrement and inhomogeneous conduction in response to AF.

DIFFERENCES IN RESPONSIVENESS OF SA AND AV NODE TO VAGAL STIMULATION.

Jerod M. Loeb, PhD; Daniel P. Dalton, BS; John M. Moran, MD. Northwestern University Medical School, Chicago, Illinois 60611.

It has recently been reported that SA node muscarinic receptors desensitize following prolonged vagal activation (VA). This study was directed toward a more clear characterization of vagally-induced desensitization at the SA node and also sought to determine whether these findings could be extended further to AV nodal conduction. Autonomically decentralized, chloralose anesthetized dogs (n=15) were instrumented to record ECG, arterial pressure and electrograms from SA node, RA, RV and His bundle. Right cervical VA for 60 sec increased initial cycle length (CL) 221% followed by a gradual recovery toward control; AH interval was maintained at 37% above control. VA on the left side increased initial CL 45% with less reversion of CL toward control; however, AH interval was maintained at 51% above control. Atrial drive increased control AH 11% and AH interval during right VA 81%, but AH prolongation was still maintained throughout the stimulation period. To rule out acetylcholine (ACh) depletion, ACh was administered before and during VA. While control CL and AH interval were lengthened by ACh, no significant CL increases occurred when ACh was given during VA; however, AH interval did prolong. Propranolol increased control CL 26% and control AH 12% but did not alter the relationship between VA and CL or AH interval. These data show that the negative chronotropic effect of ACh at the SA node is indeed diminished upon prolonged VA while the negative dromotropic effect upon AV nodal conduction remains unaltered. These results cannot be explained by innervation density, ACh depletion or catecholamine release but may reflect differences in cholinesterase activity or muscarinic receptor behavior at the SA and AV node.

TUESDAY, MARCH 17, 1981
PM
PHARMACOLOGY: ADRENERGIC BLOCKING AGENTS
2:00-3:30

LABETALOL THERAPY IN ANGINA PECTORIS AND SYSTEMIC HYPERTENSION: EFFECTS OF COMBINED ALPHA-BETA ADRENERGIC BLOCKADE

William H.Frishman, MD,FACC; Marc Kirschner, MD; Joel Strom, MD; Neal Klein, MD; Stanley Halprin, MD; Susan Goldner; Thierry LeJemtel, MD; Marcia Poland, BA; Michael Kram, BA; Roger Strair, PhD; Edmund H. Sonnenblick, MD, FACC, Albert Einstein College of Medicine, Bronx, N.Y.

The effects of oral labetalol (L), an alpha-beta adrenoceptor blocker, were evaluated in 10 patients (pts) with angina pectoris and hypertension. After 3 weeks of placebo (pl), increasing doses of L (300-1,200 mg/day) were given over 4 weeks followed by a rapid drug withdrawal phase. Anginal attack frequency and exercise tolerance (treadmill) were measured; also assessed were non-invasive indices of LV function (echo, systolic time intervals), plasma renin activity (PRA) and platelet function (aggregability). Compared to pl, the frequency of angina attacks/week was reduced with L; exercise time increased from 4.1±1.0 to 6.3±0.5 min, $p<0.01$. L lowered resting supine (sup) and standing blood pressure (BP) and heart rate (HR) in all pts; sup systolic BP 154.5±6.1 to 121.5±7.9 mmHg, $p<0.001$, sup diastolic BP 103.6±1.6 to 87.1±2.1 mmHg, $p<0.01$, sup HR 76.8±4.7 to 63.9±3.5 beats/min, $p<0.05$. The increments in systolic BP with exercise were significantly blunted, $p<0.01$, while HR increments were not affected. There was a significant reduction in resting HRxBP and an inhibition of HRxBP increments with exercise. At comparable exercise time, ECG ST segment depressions were less with L compared to pl, $p<0.05$. Compared to pl there were no effects of L on platelet function and on non-invasive indices of LV function. Pts with elevated PRA (n=3) demonstrated a marked reduction after L; pts (n=7) with normal or low PRA were not affected by L. No "rebound" effects were seen following L withdrawal. Combined alpha-beta adrenergic blockade with L is effective for relieving angina symptoms, improving exercise tolerance, and reducing elevated BP.

REDUCTION OF MYOCARDIAL ISCHEMIA BY BALANCED ALPHA AND BETA BLOCKADE WITH LABETALOL

Dietmar H. Glogar, M.D.; Robert A. Kloner, M.D., Ph.D.; Harvard Med. School/Peter B. Brigham Hosp., Boston, MA

It is known that beta blockade decreases blood flow to ischemic myocardium, but it is unknown whether this effect, which may be related to unopposed alpha stimulation, can be counteracted by additional alpha blockade. Labetalol (LAB) offers the opportunity to study both types of blockade since it has been shown to block predominantly beta receptors at 0.5 mg/kg (LAB I) and both alpha and beta receptors at 5.0 mg/kg (LAB II). Therefore, 28 anesthetized dogs received left anterior descending coronary artery occlusions. After 15 min of occlusion 7 dogs received a 5 min bolus of LAB I, 7 dogs LAB II, 14 control dogs normal saline (NS). The myocardium at risk of necrosis (MR) was determined before the intervention by an autoradiographic technique (MR I) and also at 6 hours of occlusion by Thioflavin S (MR II). Infarct size (IS) in percent left ventricle below occlusion (%LV) was determined by triphenyltetrazolium chloride stain. Regional myocardial blood flow (RMBF) was measured by microspheres before and 15 min following therapy. In LAB II vs. NS IS (%LV) was smaller (24 ± 3 vs 30 ± 2 respectively, $p<0.05$), while MR I (%LV) was not different (30 ± 2 vs 31 ± 2, p=n.s.). Only 79 ± 6% of MR I were infarcted in LAB II treated dogs vs 98 ± 4% in NS ($p<0.01$). Furthermore, RMBF immediately adjacent to the infarct increased from 0.61 ± 0.05 ml/min/g before to 0.80 ± 0.07 ml/min/g following treatment ($p<0.05$) leading to a reduction of the MR. In LAB I RMBF was decreased by the intervention from 0.60 ± 0.07 ml/min/g to 0.48 ± 0.04 ml/min/g, while no significant effect on IS was observed. Thus, the combination of alpha and beta blockade achieved by high dose labetalol (LAB II) improved coronary blood flow to the ischemic myocardium. Also, LAB decreased IS. This indicates that balanced alpha and beta blockade reached with high dose LAB may overcome secondary vasoconstriction observed in predominant beta receptor blockade.

THE EFFECTS OF MODERATE AND HIGH DOSE PROPRANOLOL ON VENTRICULAR FUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE

Kenneth G. Morris, MD, Sebastian T. Palmeri, MD, R. Edward Coleman, MD, David Shand, MD, Frederick R. Cobb, MD, Duke University and VA Medical Centers, Durham, North Carolina

Effects of moderate(160 mg/d) and high dose(480 mg/d) propranolol(P) on rest(R) and exercise(Ex) left ventricular(LV) function were determined in 14 patients with symptomatic CAD. LV function was measured by multigated radionuclide angiography(RNA) in the upright position at control and after 2 weeks on each dose. Measurements included heart rate-pressure product($R\cdot P$), ejection fraction(EF), wall motion index(WMI) determined from 3 regions graded 0-5 for normal, mild or severe hypokinesis, akinesis or dyskinesis and plasma P levels. The following lists $\bar{X}$ data ± SD at rest. *=$p < .05$ vs cont, †=$p < .05$ vs P-160.

	$R\cdot P\times10^2$	EF%	WMI	Plasma P ng/ml
Cont	102±31	57±4	1.9±1.4	
P-160	76±18*	58±6	1.4±1.8	69±41
P-480	69±15*	59±6	.86±1.0	288±136†

The following list $\bar{X}$ data and no. patients with ↓ST and chest pain(CP) at control maximum workload.

	$R\cdot P\times10^2$	EF%	ΔEF%	WMI	↓ST	CP
Cont	214±60	52±8	-5.0±.8	5.3±1.5	12	11
P-160	146±37*	56±7	-2.6±.6	3.3±2.1*	7*	5*
P-480	139±36*	57±8	-2.1±.6	2.9±2.0*	1*†	1*†

These data indicate that at pretreatment maximum workload, P-160 reduces regional dysfunction, $R\cdot P$, ↓ST and CP but does not effect global EF; P-480 did not further improve Ex LV function or reduce $R\cdot P$ despite further reduction in ↓ST and CP.

PERSISTANT MYOCARDIAL PROPANOLOL LEVELS IN MAN

John R. Plachetka, Pharm.D.; Neal W. Salomon,M.D.; Jack G. Copeland, M.D., University of Arizona, Tucson, Arizona

The physiologic effects of propanolol (P) are present after chronic oral dosing even when plasma levels are unmeasurable. The reason for this prolonged activity is unknown but may be related to large amounts of P remaining in the target organs. Since there is little information about the relationship between plasma and heart P concentrations in man,we obtained simultaneous plasma and right atrial tissue samples prior to cardiopulmonary bypass from 19 patients maintained on chronic oral P for angina. 14 pts (group I) received 0.1mg/kg P I.V. 1-2 hrs. prior to sampling and 5 patients (group II) did not get I.V. P but received their last oral dose 10-15 hrs before sampling. P in tissue homogenate extracts and plasma was assayed by fluorimetry.

There is an excellent correlation between tissue and plasma concentrations of P in group I ($r=0.943$, $p<0.001$) and group II ($r=0.992$, $p<0.001$). However, the tissue to plasma ratio was higher in group II (13.1 ± 1.73sd) than in group I (9.4 ± 3.82sd) ($p<0.05$). As the plasma levels were nearly identical, the difference was due to higher tissue levels in group II. The acute I.V. administration of P was well tolerated by all patients but one who required atropine for bradycardia.

The concentration of propanolol in heart tissue is approximately 10 times greater than that in plasma. Assuming the first-order elimination rates of P from tissue and plasma are equal, P in tissue will be present in detectable quantities twice as long as P in plasma. The prolonged action of P may be due to sufficiently high P concentrations at the myocardial beta-receptor to produce blockade even though plasma levels are undetectable.

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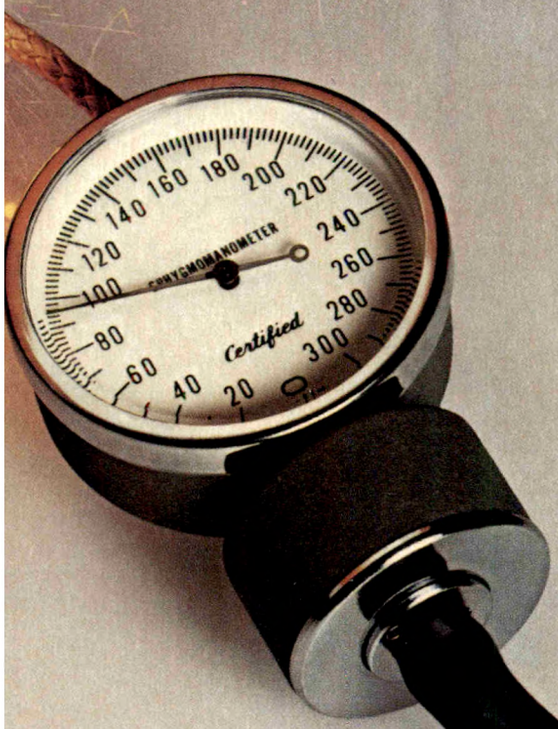

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Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn.
Usual Dose: One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:
1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H.: Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

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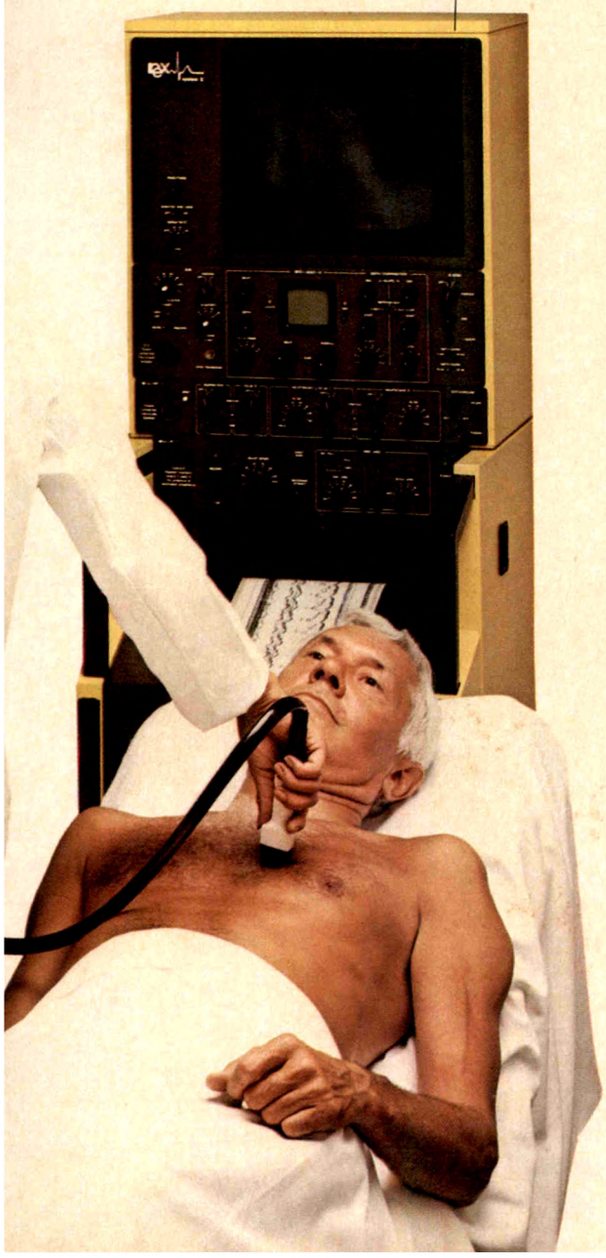

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AJC

If you can't hold
the patient,
you can't hold
the pressure
Sculpture representing the
alpha central action* of Combipres®

Alpha... hold the pressure

- central control of blood pressure*
- low incidence of impotence, depression, orthostatic hypotension**
- most common side effects are dry mouth, drowsiness and sedation, which generally tend to diminish with time. As with other agents containing diuretics, hypokalemia, hyperuricemia, and hyperglycemia may occur.

*Central alpha-adrenergic stimulation decreases sympathetic outflow from the brain, as shown in animal studies.

**Orthostatic hypotension has been reported with chlorthalidone and may be potentiated when chlorthalidone is combined with alcohol, barbiturates, or narcotics.

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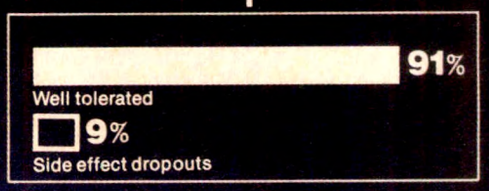
91% compliance†



†Of 484 patients in 16 clinical trials, only 9% definitely or probably dropped out due to side effects.[1]

[1] Data on file, Boehringer Ingelheim Ltd.

Please see brief summary on last page for warnings, precautions, and adverse reactions.

Combipres is not indicated for initial therapy. It is for patients responsive to its components given separately in equivalent dosages.

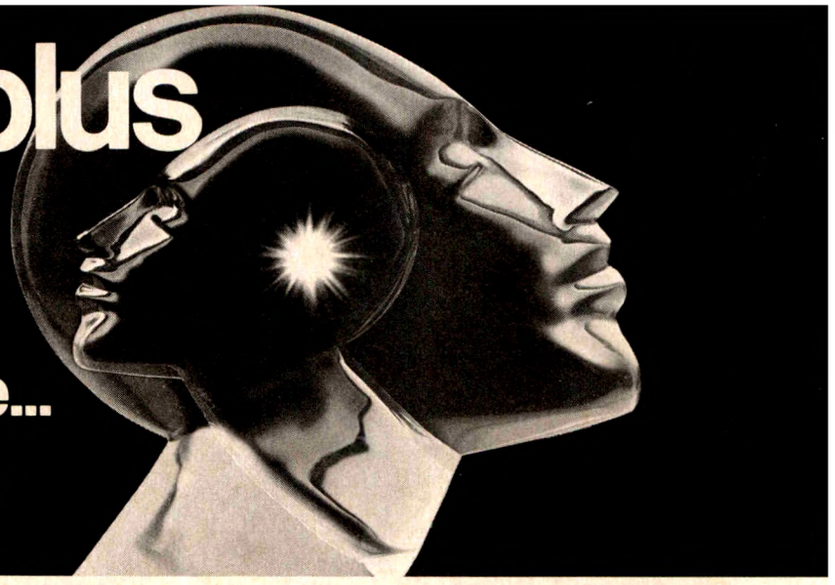
Combipres®

Each tablet contains: Catapres® (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

.1 and .2

Hypertension

Alpha...plus



hold the pressure... hold the patient...

Combipres® .1 and .2

Each tablet contains: Catapres® (clonidine HCl) 0.1 or 0.2 mg, and chlorthalidone, 15 mg

Warning: This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Indication: The drug is indicated in the treatment of hypertension (see box warning).

Contraindications: Patients with known hypersensitivity to chlorthalidone and patients with severe renal or hepatic diseases.

Warnings: Tolerance may develop in some instances necessitating a reevaluation of therapy.

Usage in Pregnancy: In view of embryotoxicity findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefit outweighs the potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of Combipres in children.

Precautions: When discontinuing Combipres, reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of Combipres therapy or by intravenous phentolamine.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect of the clonidine hydrochloride component. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other antihypertensive agent, Combipres should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Combipres should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmological findings have been recorded with Catapres, in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Patients predisposed toward or affected by diabetes should be tested periodically while receiving Combipres, because of the hyperglycemic effect of chlorthalidone.

Because of the possibility of progression of renal failure, periodic determination of the BUN is indicated. If, in the physician's opinion, a rising BUN is significant, the drug should be stopped.

The chlorthalidone component of Combipres may lead to sodium and/or potassium depletion. Muscular weakness, muscle cramps, anorexia, nausea, vomiting, constipation, lethargy or mental confusion may occur. Severe dietary salt restriction is not recommended in patients receiving Combipres.

Periodic determinations of the serum potassium level will aid the physician in the detection of hypokalemia. Extra care should be given to detection of hypokalemia in patients receiving adrenal corticosteroids, ACTH or digitalis. Hypochloremic alkalosis often precedes other evidence of severe potassium deficiency. Frequently, therefore, more sensitive indicators than the potassium serum level are the serum bicarbonate and chloride concentrations. Also indicative of potassium depletion can be electrocardiographic alterations such as changes in conduction time, reduction in amplitude of the T wave; ST segment depression; prominent U wave. These abnormalities may appear with potassium depletion before the serum level of potassium decreases. To lessen the possibility of potassium deficiency, the diet, in addition to meat and vegetables, should include potassium-rich foods such as citrus fruits and bananas. If significant potassium depletion should occur during therapy, oral potassium supplements in the form of potassium chloride (3 to 4.5 gm/day), fruit juice and bananas should be given.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy.

Clonidine hydrochloride: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one case of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash; impotence, urinary retention; increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Chlorthalidone: Symptoms such as nausea, gastric irritation, anorexia, constipation and cramping, weakness, dizziness, transient myopia and restlessness are occasionally observed. Headache and impotence or dysuria may occur rarely. Orthostatic hypotension has been reported and may be potentiated when chlorthalidone is combined with alcohol, barbiturates or narcotics. Skin rashes, urticaria and purpura have been reported in a few instances.

A decreased glucose tolerance evidenced by hyperglycemia and glycosuria may develop inconsistently. This condition, usually reversible on discontinuation of therapy, responds to control with antidiabetic treatment. Diabetics and those predisposed should be checked regularly.

As with other diuretic agents hypokalemia may occur (see Precautions). Hyperuricemia may be observed on occasion and acute attacks of gout have been precipitated. In cases where prolonged and significant elevation of blood uric acid concentration is considered potentially deleterious, concomitant use of a uricosuric agent is effective in reversing hyperuricemia without loss of diuretic and/or antihypertensive activity.

Idiosyncratic drug reactions such as aplastic anemia, thrombocytopenia, leukopenia, agranulocytosis, and necrotizing angiitis have occurred, but are rare.

The remote possibility of pancreatitis should be considered when epigastric pain or unexplained gastrointestinal symptoms develop after prolonged administration.

Other adverse reactions which have been reported with this general class of compounds include: jaundice, xanthopsia, paresthesia and photosensitization.

Overdosage: *Catapres (clonidine hydrochloride):* Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals abolishes all effects of Catapres overdosage.

Chlorthalidone: Symptoms of overdosage include nausea, weakness, dizziness, and disturbances of electrolyte balance. There is no specific antidote, but gastric lavage is recommended, followed by supportive treatment. Where necessary, this may include intravenous dextrose and saline with potassium administered with caution.

How Supplied: Combipres® 0.1 (Each tablet contains clonidine hydrochloride 0.1 mg + chlorthalidone 15 mg). It is available as pink, oval, single-scored compressed tablets in bottles of 100.

Combipres® 0.2 (Each tablet contains clonidine hydrochloride 0.2 mg + chlorthalidone 15 mg). It is available as blue, oval, single-scored compressed tablets in bottles of 100.

For complete details, please see full prescribing information.

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VENTRICULAR FIBRILLATION THRESHOLD DURING PROPRANOLOL WITHDRAWAL

Zvi Ziskind, MD; Aram Smolinsky, MD: Daniel A. Goor, MD; Dept. of Cardiac Surgery, Sheba Medical Centre, Sackler School of Medicine, University of Tel-Aviv.

Abrupt propranolol withdrawal is known to cause increased ventricular excitability in general patients and those post aorto-coronary bypass. The electrophysiological aspect of this phenomenon was investigated in the present study by measuring the ventricular fibrillation threshold (VFT) in dogs subjected to such treatment. Eight dogs received propranolol, 3 mg/kg daily, p.o., for two weeks, after which the drug was abruptly discontinued. 48 hours later the VFT was measured as the current required to induce ventricular fibrillation in two stimulation methods: 1) single constant current pulse, synchronized to occur during the vulnerable period; and 2) a train of pulses at 60 Hz, synchronized to occur 50-450 msec after the QRS. Ten dogs served as control. While on propranolol, the dogs' heart rate (HR) slowed from 115 (±5) to 77 (±4). 48 hours after drug withdrawal the HR rose to 159 (±11). Using single pulse stimulation, VFT decreased from 31 ± 2.16 mamp - control group, to 11.2 ± 1.8 mamp - propranolol withdrawal group. Using train of pulses stimulation, VFT decreased from 5.28 ± 0.95 - control group to 1.54 ± 0.32 - test group. This threefold drop in VFT compared to control values is highly significant ($p<0.001$, t-test) and points to an additional hazard of abrupt propranolol discontinuation.

PREVENTION OF POSTOPERATIVE SUPRAVENTRICULAR TACHYARRHYTHMIA IN CORONARY BYPASS PATIENTS, WITH LOW-DOSE PROPRANOLOL

Rephael Mohr, MD; Aram Smolinsky, MD; Daniel A. Goor, MD; Dept. of Cardiac Surgery, Chaim Sheba Medical Centre, University of Tel-Aviv, Israel.

The increased tendency of patients (pts) to develop supraventricular tachyarrhythmia (SVT) after aorto-coronary bypass (ACBP) is attributed to supersensitivity after Propranolol withdrawal. This study examined the effect of early readministration of Propranolol via nasogastric-tube, on the incidence of postoperative SVT. Eighty-five consecutive pts receiving long-term Propranolol therapy were randomized after ACBP to either receive mini-dose Propranolol (Group I) or serve as controls (Group II). They were compared with 18 pts (Group III) who did not receive beta-blockers prior to surgery, but were given Propranolol postoperatively. Poor risk pts (left ventricular aneurysms, low ejection fraction, congestive heart failure) were included in the study. All 3 Groups were comparable on all risk factors. Propranolol (5-10 mg orally every 6 hrs) was started through nasogastric-tube 6 hrs after surgery & continued orally in pts of Groups I & III. SVT appeared in 2 of 37 pts in Group I (5%), 19 of 48 pts in Group II (40%) & 5 of 18 pts in Group III (27%). The incidence of SVT was significantly lower in Group I than in Groups II & III ($p<0.001$ Group I vs. Group II, $p<0.01$ Group I vs. Group III). These results show that early reinstitution of low-dose Propranolol following ACBP can prevent SVT in pts receiving beta-blocking agents preoperatively.

TUESDAY, MARCH 17, 1981
PM
SURGERY FOR CONGENITAL HEART DISEASE: FOLLOW-UP STUDIES
2:00-3:30

ECHOCARDIOGRAPHIC AND ANGIOCARDIOGRAPHIC FEATURES BEFORE AND AFTER THE JATENE PROCEDURE(ARTERIAL SWITCH)FOR TRANSPOSITION OF THE GREAT ARTERIES.

Walter J. Duncan,MD,;Peter M.Olley,MD,FACC;Richard D.Rowe, MD,FACC;Robert M.Freedom,MD,FACC;William G.Williams,MD; George A.Trusler,MD. The Hospital for Sick Children, Toronto,Ontario,Canada.

Eight patients with transposition of the great arteries (d-TGA)and associated anomalies have undergone Jatene's procedure with correction of associated anomalies.Six patients survived and were studied pre and post operatively by M-mode(M)and two-dimensional echocardiography(2DE) as well as by cardiac catheterization(C)and angiography (A).Pre-operative M studies showed panchamber enlargement and diagnosed d-TGA in all.Left ventricular outflow tract (LVOT)narrowing was present in 2 patients-one of these also had systolic anterior mitral motion(SAM).2DE confirmed the additional features of isolated ventricular septal defect(VSD)in 2 patients;double outlet right ventricle in 2,patent ductus arteriosus in 2 and right atrio-ventricular valve atresia(TA)in 2.Post operatively, M showed normal systemic ventricular function in 5 patients.No patient showed LVOT narrowing or SAM.Right ventricular(RV)size was increased in 4 patients(RV remained small in both patients with TA).2DE showed patent coronary ostia in all and no dysynchronous wall motion was apparent except in the area of the VSD patch.C and A have confirmed good results in all but one patient who had impaired ventricular function pre operatively.One patient has stenosis of the right coronary ostium by A--2 have mild aortic regurgitation.None have significant LVOT gradients and only one has a significant right ventricular outflow tract gradient(47mmHg).In summary,M,2DE,C and A all contribute to assessment of patients before and after the Jatene procedure.

RADIONUCLIDE ASSESSMENT OF LEFT VENTRICULAR FUNCTION IN PATIENTS WITH TRICUSPID ATRESIA

Joyce R. Harder, MD; David L. Gilday, MD; Margaret deSouza, MA; Robert M. Freedom, MD, FACC; Peter M. Olley, MD, FACC; Richard D. Rowe, M.D, The Hospital for Sick Children, Toronto, Canada.

Accurate evaluation of LV function in patients with tricuspid atresia (TAT) has become necessary since the introduction of the Fontan and similar operations. We have used multiple gated blood pool analysis (MUGA) to assess LV ejection fraction (EF) at rest, and during exercise (EX) in 20 patients with TAT. Age ranged from 6.5 to 22 years, median 10 years. Eleven patients were male and 9 female. Resting EF was normal in 13 patients (mean 63.6 ± 5.3%) Group 1, and abnormal in 7 (mean 47.7 ± 5.6%) Group 2. Eleven patients in Group 1 increased EF during EX (mean 7.4 ± 2.5%), 2 showed a decrease. EX EF in Group 2 fell in 5 patients and increased slightly in 2. No ST segment depression was noted in any patient with an EX EF increase of greater than 5%. Of the 2 patients in Group 1 with a drop in EX EF, only 1 showed ST segment depression. In Group 2 5/7 patients demonstrated ST segment change. Mean age of patients in Group 1 was 13.7 ± 5 years as compared to 14.6 ± 3 years in Group 2. Mean resting 0_2 saturation did not differ significantly between the groups. Prior surgical procedures included multiple shunts in 11 patients, Glenn only in 4, Fontan in 4. Mean resting EF in each surgically treated subgroup did not differ significantly. These results suggest that 1) MUGA is a valuable noninvasive means to evaluate LV function in patients with TAT, 2) response to exercise may be abnormal when resting EF is normal, 3) ST segment change is not consistently present with decreased exercise EF, 4) in our study LV function is relatively well preserved and abnormal function is not related to age, prior surgical procedures, or resting oxygen saturation.

HEMODYNAMIC EVALUATION OF THE FONTAN PROCEDURE AT REST AND WITH EXERCISE

William E. Hellenbrand, MD; Hillel Laks, MD; Charles S. Kleinman, MD; Norman S. Talner, MD, Yale University School of Medicine, New Haven, CT

Hemodynamic assessment was performed in seven patients (pts) one year following a Fontan procedure. The diagnoses included tricuspid atresia (4), pulmonary atresia (1), mitral atresia (1) and a criss-cross heart (1). Mean age at operation was 15 (8-21 years). At surgery, a 25 mm porcine conduit was interposed between the right atrium (RA) and the right ventricle (RV) in three pts and between the RA and pulmonary artery (PA) in 4. The tricuspid valve was closed in 2 pts and the RA partitioned in one. There was an SVC-RPA anastomosis present in 3 pts. Five of the seven pts were asymptomatic with two in a chronic low output state. Hemodynamic evaluation was performed at rest and during supine exercise. At rest, mean cardiac index (CI) was 2.0 L/min/M^2 with RA-PA conduits and 2.7 L/min/M^2 with RA-RV conduits. Right atrial mean pressure averaged 20 mmHg in RA-PA conduits and 10 mmHg in RA-RV conduits. An "a" wave gradient was present across the porcine valve in the RA-RV conduits ranging from 2 to 10 mmHg with no pressure difference in the RA-PA conduits. Left ventricular ejection fraction was low normal with a mean of 0.55. During exercise, CI increased from 2.7 to 4.1 L/min/M^2. The entire augmentation in systemic flow was dependent on the change in heart rate. Mean right atrial pressure increased from 11 to 19 mmHg. When changes in cardiac output were related to oxygen consumption during exercise all pts were abnormal with a mean exercise factor of 4 (normal > 6). Continuous antegrade flow into the pulmonary arteries was present during systole and diastole in 6 pts. Despite clinical improvement following the Fontan operation abnormal hemodynamics are present at rest and become more significant with exercise.

REST AND EXERCISE HEMODYNAMICS AFTER FONTAN PROCEDURE.

Giora Ben Shachar, MD, Bradley P. Fuhrman, MD, Yang Wang, MD, Russell V. Lucas, MD, James E. Lock, MD; University of Minnesota, Minneapolis, Minnesota.

Sixteen patients, aged 5-26, underwent a Fontan procedure with no operative deaths. Two late deaths were sudden and unexpected. Marked clinical improvement occurred in most survivors; 11 of 14 were NYHA class I or II. Eleven of the 14 agreed to postop catheterization. Four had developed right-to-left shunts through an oversewn atrioventricular valve ring, invalidating CI measurement. Hemodynamic data on the remaining 7 patients, including 4 at both rest and exercise, were compared to published results in normals of similar age. None of the exercised patients had a previous Glenn anastomosis; all were NYHA class I.

Fontan:	N	C.G. mmHg	Mean RA Pressure mmHg	C.I. L/min/M^2	Stroke Index ml/min/M^2	PA O_2 Saturation (%)
Rest	7	2±1	14±3*	2.3±0.3*	29±6*	64±10*
Pre-exercise	4	2±1	14±2*	2.4±0.3*	30±8*	68±9
Exercise	4	8±5	26±4*	4.8±1.2*	33±14*	32±7*
Normal rest	23	-	4±2	4.4±0.7	53±10	76±4
" exercise	23	-	3±3	8.0±1.3	57±11	50±10

At rest, the CI (Fick) was low due to a small stroke index, despite normal PA pressures and a minimal conduit gradient (CG). Exercise resulted in marked PA desaturation, small rise in CI, and the appearance of a variable (5-13) but significant CG.

Despite substantial clinical improvement after Fontan procedure, these data demonstrate a decreased CI both at rest and at exercise. Further, marked RA hypertension and functional conduit obstruction occur with exercise, even in patients with favorable clinical results. The long-term implications of these results are unknown. (Data are mean ± S.D. *$p<0.05$ when compared with normal).

LATE RESULTS OF OPERATION FOR DISCRETE SUBAORTIC STENOSIS

Glenn R. Barnhart, M.D.; Michael Jones, M.D.; Andrew G. Morrow, M.D., National Heart Institute, Bethesda, Md.

Between 1956 and 1979 we performed complete resection of the fibrous ring in 53 patients with discrete subaortic stenosis. Six patients had associated anomalies: PDA, VSD, RV outflow obstruction, and/or Ao to RV fistula. Five patients suffered perioperative deaths; 4 were during our very early experience. Excluding 12 foreign patients, late follow-up evaluations including cardiac catheterizations were performed at our institution for all 36 survivors 1 to 24 years (mean 12.2 years) postoperatively. Gradients preoperatively averaged 98 mm Hg (35-190); gradients at 2 to 168 months (mean 18 months) postop averaged 38 mm Hg (0-200). Eight patients had residual gradients over 50 mm Hg, of whom 6 had the tunnel form of LV outflow obstruction. There were 6 late cardiac deaths. Of the long-term survivors 23 of 30 are asymptomatic. Six patients have required reoperation, and 3 patients have developed bacterial endocarditis. Aortic regurgitation was present in 22 patients preop; 5 additional patients have it late postop. Cardiothoracic ratios averaged 0.53 preop and 0.44 late postop. ECG criteria for LVH were present in 26 patients preop and in 10 late postop. Average echocardiographic LV systolic and diastolic dimensions were normal late postop, 30 and 49 mm, respectively. Actuarial survival is 94% at 5 years (n=28), 87% at 10 years (n=22), and 81% at 20 years (n=7). Survival without adverse cardiac abnormalities (reoperation, bacterial endocarditis, residual gradient >50 mm Hg, cardiothoracic ratio >than 0.60, or definite LVH by ECG criteria) is similar at 5 years (54%) and at 10 years (55%). We conclude that resection relieves symptoms and obstruction and gives satisfactory late results for most patients with discrete subaortic stenosis, but residual cardiac abnormalities require continuing long-term follow-up.

TETRALOGY OF FALLOT: 11 YEAR EXPERIENCE IN NEW ENGLAND

Lucy P. Buckley, MD and Donald C. Fyler, MD, FACC, New England Regional Infant Cardiac Program, Children's Hospital Medical Center, Boston, MA

Over the past 11 years, 407 of 4,505(9%) infants born in New England with critical congenital heart disease had tetralogy of Fallot(TF) as their major cardiac malformation. Despite a 25% drop in birthrate, the number of new patients over the years did not vary and case discovery increased from .18 to .25 per 1000 live births. Overall, 102 of 407(25%) infants died before their first birthday and the loss was twice as great among the 87 infants admitted within the first 48 hours of life. As expected, mortality was greater among those with associated cardiac lesions: coronary abnormalities(20), absent pulmonary valve(13), absent pulmonary artery(8), arch anomalies (10) aortic and mitral problems(9), congenital complete heart block(3), total anomalous pulmonary venous return(2), cor triatriatum (1), aorticopulmonary window(1), juxtaposition atrial appendages(1) and Ebstein's anomaly(1). When the 118 of 407 (29%) "high risk" infants with low birthweight (<2.5kg) and/or severe associated anomalies were excluded, first year medical mortality was halved but surgical mortality was unchanged.

Among the 313 infants with TF, 187 (60%) were managed surgically: operative mortality was 17%(18 of 108) for palliative shunts and 26%(19 of 74) for primary repair. Mortality was significantly higher among the 94 infants with pulmonary atresia with ventricular septal defect: shunt mortality was 30%(16 of 54) and 2 of 3 died at attempted repair. Of the 45 infants operated in 1968-69, 42 were shunted and 14(31%) died, whereas of the 43 infants operated in 1977-78, 25 were repaired and 4(9%) died.Comparison of surgical experience over time suggests that primary repair of TF syndrome in the first year of life is superior to palliative shunting and later repair.

TUESDAY, MARCH 17, 1981
PM
INTRACARDIAC ELECTROPHYSIOLOGIC STUDIES
2:00-3:30

RESULTS OF PROGRAMMED STIMULATION IN 80 PATIENTS HAVING A HISTORY BUT NO ELECTROCARDIOGRAPHIC DOCUMENTATION OF TACHYCARDIA.

Hein J.J. Wellens, MD, FACC; Frits W.H.M. Bär, MD; Eddy J.D.M. Vanagt, MD; Pedro Brugada, MD; Willem R.M. Dassen, PhD, Dept. of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands.

Identification of site of origin and mechanism of tachycardia(T) is important for proper selection of therapy. Therefore 80 consecutive patients(P) having a history of paroxysmal T but no electrocardiographic documentation were studied by programmed electrical stimulation(PES) of the heart. If no T could be initiated during PES, Atropine was given and PES repeated.
Results: Sustained T could be initiated by PES in 53 P (66%). Site or origin of T was: Atrial 8, AV-nodal: 19 (in 7 P T could only be initiated after Atropine), Ventricular: 6. In 5 P a concealed accessory pathway was used during T. In all 15 P showing a WPW electrocardiogram a circusmovement T with atrio-ventricular conduction over the AV-node and ventriculo-atrial conduction over the accessory pathway could be initiated by PES.
Conclusions: 1) In all 15 P having a WPW electrocardiogram and a history of T a circusmovement T could be initiated during PES. 2) In the remaining 65 P sustained T could be initiated in 38 P (= 58%). 3) T originated in different sites in the heart, AV-nodal T being the most common type.

THE ELECTROPHYSIOLOGIC ASSESSMENT OF PATIENTS WITH SYNCOPE

Robert O. Brandenburg, Jr., MD; David R. Holmes, Jr., MD, FACC; Geoffrey O. Hartzler, MD, FACC, Mayo Clinic, Mayo Foundation, Rochester, MN.

From 1977 to 1980, 92 patients (pts) with syncope of unknown etiology underwent invasive electrophysiologic (EP) studies to determine the mechanism of their syncope. Prestudy investigations including 12-lead electrocardiography (92 pts), 24 hour Holter monitoring (75 pts), exercise testing (24 pts), and neurologic assessment including electroencephalograms (63 pts) had failed to identify an etiology in any patient. There were 55 males and 37 females (mean age 58 years) with a mean of 9.1 episodes of syncope per patient which had occurred over a mean of 20.8 months prior to the EP study.

EP testing documented a probable cause for syncope in 59 of the 92 pts (64%). The most common abnormality was identifiable His-Purkinje conduction system disease which was found in 14 pts. The remaining pts were found to have carotid sinus hypersensitivity (11 pts), hypervagotonia (10 pts), ventricular dysrhythmias (10 pts), supraventricular tachycardia (9 pts), and intrinsic sinus node dysfunction (5 pts). Based on the EP testing, therapy directed at the specific mechanism of syncope was initiated. Follow-up data was available for 54 of the 59 pts (91%). During a mean follow-up of 14.2 months (range 4 to 38 months), 48 pts (89%) remained free of syncope on treatment. Two additional pts (4%) were improved on treatment but still had symptoms. The remaining 4 pts remained unchanged and in one of these an additional mechanism for syncope was documented.

We conclude that EP testing plays a valuable role in the evaluation of pts with syncope of unknown etiology. It may identify the potential mechanism for syncope and facilitates selection of specific treatment modalities.

UNEXPLAINED SYNCOPE: RESULTS OF THERAPY BASED ON ELECTROPHYSIOLOGIC STUDIES.

JOHN P. DIMARCO, MD, HASAN GARAN, MD, J. WARREN HARTHORNE, MD, FACC, JEREMY N. RUSKIN, MD, FACC. MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS.

Twenty-one patients with recurrent syncope that remained unexplained after thorough medical and neurologic evaluations underwent intracardiac electrophysiologic study (EPS) with atrial and ventricular programmed stimulation (PS). Patients with bifascicular block and 1° AV block on baseline ECG were excluded. Syncope had been present for from 3-96 months and each patient had had 3 or more prior episodes. Results of EPS were considered diagnostic in 6 patients with rapid ventricular tachycardia [271±11 (mean ±S.D.) beats per minute] induced by PS, in 3 patients with intra-His conduction delays, in 1 patient with induced atrial flutter and a rapid ventricular rate, and in 1 patient with sinus node dysfunction and induced atrial flutter. In 3 other patients, EPS revealed a persistent prolongation of AV nodal refractoriness that was reversible with atropine suggesting increased vagal tone as a possible mediator for syncope. Based on these findings at EPS, therapy was instituted with either antiarrhythmic drugs (8 patients), ventricular pacing (5 patients), or both (1 patient) with complete relief from recurrent syncope in 12 patients, marked improvement in 1 patient, and no change in 1 patient over 17.8± 5 months of follow-up. Syncope persists and remains unexplained in 3 of the 7 patients in whom EPS did not suggest an etiology. These observations indicate that EPS with PS should be utilized in the diagnostic evalaution of selected patients with recurrent unexplained syncope, since such testing may reveal arrhythmias or conduction system disease which are not demonstrable by noninvasive techniques. Specific prophylactic therapy directed against abnormalities detected by electrophysiologic testing is highly effective in preventing the recurrence of syncope.

NODAL FUNCTION IN 30 PATIENTS WITH ATRIOVENTRICULAR NODAL 1/1 CONDUCTION ABOVE 200/MN.

Robert Frank, M.D., Guy Fontaine, M.D., Hoan Phan-Thuc, M.D., Patrick Blanc, M.D.
Hôpital de la Salpêtrière, Paris, France.

In normal adults, it has been considered that 1:1 conduction of atrial impulses to the ventricles above a rate of 200/mn is indicative of an atrioventricular (AV) nodal bypass tract. In order to examine this contention, we reviewed the records of 600 consecutive adult patients who had electrophysiologic study and found 30 with 1:1 AV nodal conduction at atrial rates above 200/mn.

Under basal conditions, the AH time was abnormally short (50ms or less) in 22 cases. The nodal effective refractory period was normal for the cycle length in 9, and could not be assessed in 21 because it was atrial limited. The nodal functionnal refractory period was normal in all. H1H2 vs A1A2 curve by the extrastimulus techniques was normal in 15, 5 had a plateau, 4 had a dual curve and 6 were undetermined. AH vs RR curve with atrial pacing by step of increasing rates had a constant slope in 15, 8 had 2 or 3 slopes and 7 had a plateau followed by a slope. In none of these 30 patients could AV nodal reentrant supraventricular tachycardia be induced.

Vagal stimulation was provoqued in each patient by injection of ATP (10 or 20mg IV bolus). In each patient first and second degree AV block occured within the AV node.

Therefore 1) since AV conduction prolonged or ceased in all patients with vagal stimulation, we concluded that an extranodal bypass tract was not responsible for an enhanced AV conduction, 2) enhanced AV conduction is not a prediction of AV reentrant supraventricular tachycardia, 3) an "enhanced" AV conduction may be due to a great variety of nodal responses.

IITIATION OF ATRIO-VENTRICULAR NODAL RE-ENTRANT TACHY-
ARDIA IN PATIENTS WITH DISCONTINUOUS ANTEGRADE CONDUC-
ION CURVES. IMPORTANCE OF A DISCONTINUOUS RETROGRADE
ONDUCTION CURVE.

edro Brugada, MD; Eddy J.D.M. Vanagt, MD; Frits W.H.M.
ir, MD; Willem R.M. Dassen, PhD; Hein J.J. Wellens, MD,
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o study factors playing a role in initiation of sustained
rio-ventricular nodal tachycardia(S AVN T), antegrade
A) and retrograde(R) conduction curves(CC) were determined
sing the extrastimulus technique at 2 different basic cycle
engths(BCL) in 25 patients(pts) without accessory pathway.
s were grouped according to: Discontinuous(D) ACC and
ontinuous RCC at both BCL (GROUP 1, 14 pts), or DACC at
oth BCL and DRCC at 1 or 2 BCL (GROUP 2, 11 pts). Mode of
nitiation of S AVN T - 1 atrial premature beat(APB),
ultiple(M) APB, or atrial pacing at increasing rates(IR)-
as studied in both groups. If S AVN T was not initiated,
ng atropine(ATR) was given intravenously and the study
epeated.

ESULTS: Number of pts and mode of initiation of S AVN T

ROUP	1 APB	MAPB	IR	AFTER ATR
1	13/14	-	-	1/1
2	1/11	1/10	0/9	6/9

here was a significant difference in: a) initiation of S
VN T by a single APB, b) need of ATR administration to
nitiate S AVN T, c) relation between the longest A-H
nterval of the slow A-V nodal pathway and the value of
he R refractory period of the fast pathway, and d) elec-
rocardiographic documentation of the arrhythmia (12 in
roup 1, 1 in group 2).
ONCLUSIONS: 1) Initiation of S AVN T is unlikely in the pre-
ence of a DRCC unless ATR is used. 2) Pts with documented
have a shorter R refractory period of their fast A-V nodal
athway.

NALYSIS OF ANTEGRADE AND RETROGRADE FAST PATHWAY
ROPERTIES IN DUAL PATHWAY PATIENTS

obert Bauernfeind, MD, FACC; Steven Swiryn, MD, FACC;
hristopher Wyndham, MD, FACC; Boris Strasberg, MD; Edwin
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llinois, Chicago, Illinois.

n a previous study, we found an unexpectedly high preva-
ence (17%) of short PR among patients (pts) with dual
athway (DP) AV nodal reentrant tachycardia (PSVT). One
equirement for PSVT is that the retrograde (R) fast path-
ay (FP) have the ability to sustain sequential conduction
SC). In the present study, we examine SC of antegrade
A) and R FP as functions of AH interval (FP conduction
ime during sinus rhythm). In 160 pts with DP (with and
ithout PSVT), AH ranged from 46 to 234 msec (mean $\pm$ SD,
1 $\pm$ 30). Incremental atrial pacing was used to assess
FP SC. Slowest paced cycle lengths (CL) at which AFP SC
ailed (resulting in slow pathway conduction) ranged from
73 to 857 msec (438 $\pm$ 112). Regression analysis of these
L vs AH revealed $r = 0.40$ ($p < 0.01$). Incremental ventric-
lar pacing was used to assess RFP SC in 123 pts. Intact
SC was present in 91 pts and absent in 32 pts, being
resent in 15/15 pts with AH $<$ 60, 70/98 pts with AH 60-
30, and 6/10 pts with AH $>$ 130 ($p < 0.05$). Intact R SC was
resent at CL $\leq$ 400 in 11/15 pts with AH $<$ 60, 44/98 pts
ith AH 60-130, and 2/10 pts with AH $>$ 130 ($p < 0.05$). In
onclusion, there is a relationship between AH and ability
f AFP for SC (pts with shorter AH having better AFP SC).
here is a similar relationship between AH and ability of
FP for SC, implying that RFP is same pathway as AFP. In
population of pts with DP, pts with shorter AH (and PR)
re predisposed to PSVT, by virtue of better SC of RFP.

TUESDAY, MARCH 17, 1981
PM
ADVANCES IN PACING
2:00-3:30

EVALUATION OF PACING FUNCTION BY REAL TIME TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Bapineedu Gondi, MD, Navin C. Nanda, MD, FACC, University of Rochester Medical Center, Rochester, NY

Our experience in 101 patients (pts) with pacing catheters has demonstrated the usefulness of two-dimensional echocardiography (2D echo) in the evaluation of pacing function (ATL 90° sector scanner). 2D echo provided direct evidence for myocardial wall perforation by temporary pacing catheters (PCs) in 5 pts. In 3 pts with loss of sensing and/or increased pacing threshold the PCs were seen penetrating RV apex with the tip lying 2 mm to 1 cm outside the heart border. In 1 pt the PC was repositioned under 2D echo control in another area of RV apex with decrease in pacing threshold from 15mA to 0.5mA. Pericardial effusion was observed in 2 pts, in one of whom it was localized to the site of perforation; neither pt showed cardiac tamponade. The 4th pt showed perforation of the atrioventricular septum with the PC in LV and the 5th pt showed partial penetration of ventricular septum. Both showed right bundle branch block pattern and the withdrawal intracardiac ECG was typical of perforation in the 5th pt. In 4 of 5 pts the identification and abnormal location of the PC was confirmed during PC withdrawal when movements of the PC could be seen to correspond with manual manipulations. Perforation was verified at autopsy in 2 pts, including 1 pt in whom PC was not withdrawn. In 1 of 4 pts with epicardial PC the tip was seen extending into the ventricular chamber (reverse perforation). PC displacement into a hepatic vein was diagnosed in 1 pt in whom chest X-ray suggested myocardial wall perforation. Lead breakage near the pulse generator was detected in 1 pt with intermittent capture. We also found 2D echo useful to accurately position catheters in the RV apex (2 pts) and below the tricuspid valve in contact with ventricular septum for His bundle recordings (2 pts).

P SYNCHRONOUS PACING: A NEW ORTHOGONAL APPROACH TO P-WAVE SENSING

BN Goldreyer, MD, FACC; AL Olive; J Leslie; DS Cannom, MD, FACC; MG Wyman, MD, FACC; San Pedro Peninsula Hospital, San Pedro, California.

P synchronous pacing has long been identified as advantageous for patients with AV conduction defects and intact sinus node function. Prior endocavitary systems have been infrequently employed, because of unreliable P wave sensing from standard ring electrodes in the atrium or the requirement for a second atrial sensing lead. A single endocardial lead employing a unipolar ventricular stimulating electrode and an orthogonal P wave sensing design was developed and tested in 22 patients undergoing electrophysiologic study or pacemaker implantation.

Thirteen cm from the stimulating tip of a standard permanent pacing lead, 3 or 4 electrodes with a surface area of 1 mm^2, equidistant from the tip were placed circumferentially about the catheter. With the catheter tip normally placed in the RV apex, atrial sensing electrodes were positioned in the mid-high lateral RA, adjacent to, but not affixed to the RA wall. Bipolar orthogonal leads X and Y were obtained. In 22 patients, during sinus rhythm, atrial electrogram voltages in the X axis of 2.47 $\pm$ 1.6 mv and 2.32 $\pm$ 1.6 mv in the Y axis were recorded. QRS voltages of 0.078 mv and 0.073 mv respectively allowed dramatic ability to discriminate P from QRS complexes (P/QRS = 32/1). There was no change in QRS voltages recorded during spontaneous PVC's, bipolar or unipolar ventricular pacing.

A single catheter designed for P synchronous pacing employing circumferentially placed atrial sensing electrodes has demonstrated unique atrial sensing voltages with excellent QRS signal rejection.

GATED RADIONUCLIDE ANGIOGRAPHY DURING UPRIGHT EXERCISE IN PATIENTS WITH PROGRAMMABLE PACEMAKERS

Richard Steingart, MD; Corine Yee, MD; John Wexler, MD, PhD; Larry Weinstein, MD; Robert Bontemps, BS; Seymour Furman, MD, FACC, Montefiore Hospital and Medical Center, Bronx, NY

Present generation programmable pacemakers allow for non-invasive selection of a wide range of pacing rates. However, the choice of pacing rate is often arbitrary, or dictated by symptomatic complaints that may be non-specific. Gated radionuclide angiography (GRA) is an accurate, reproducible method for quantitating EF, relative cardiac output (CO), stroke volume (SV), end diastolic volume (EDV) and end systolic volume (ESV) at rest and during exercise and therefore may provide a means to determine optimal, individualized pacing rates. Pts. with fixed bradycardias undergoing programmable ventricular pacemaker implantation were selected for study. After in vivo red cell labeling with 20 mCi of 99mTc, upright GRA was performed at rest and during low level bicycle exercise (75 kilopond-meters) at the baseline pacing rate (69±4 beats/min). The rest-exercise protocol was then repeated at pacing rates 20 beats/min above and below baseline. The entire procedure required less than 1 hour for completion and was performed as early as 24 hours after pacemaker implantation. In a representative study of a pt. with coronary artery disease, at rest in the upright posture, relative CO was not influenced by changing the pacing rate as EDV and SV varied inversely with heart rate. However, both EDV and ESV rose during exercise at all heart rates with a resultant increase in CO of 20% at a heart rate of 85 beats/min, and a 48% decrease in CO at a heart rate of 45 beats/min when compared with values during exercise at 65 beats/min.

We conclude that rest-exercise GRA is a valuable aid in determining optimal pacing rates in selected patients undergoing programmable pacemaker implantation.

AUTODECREMENTAL ATRIAL PACING FOR TACHYCARDIA TERMINATION-A CLINICAL EVALUATION

John Camm,MB;Anthony Nathan,MB;Kevin Hellestrand,MB; David Ward,MB;Roworth Spurrell,MD,FACC. St.Bartholomew's Hospital,London,England.

Autodecremental atrial pacing was assessed during electrophysiological study in 20 consecutive patients with recurrent supraventricular tachycardia(T).8 had intranodal T and 12 had atrioventricular T.T cycle length ranged from 250 to 420(mean 351)msec.
The system consists of sensing and pacing circuits controlled by a small computer.T is defined as 8 successive P-P intervals less than a preset value.The first pacing cycle interval is the T cycle length minus a decrement value(D).Each subsequent pacing cycle is further reduced by the same value of D.The maximum pacing rate is 100 beats/min faster than T,with an absolute limit of 275 beats/min.Several durations of pacing (P) were assessed. If T continues,pacing resumes after 8 cycles with a different value of either P or D or both,21 different combinations were evaluated(with P:500,1000,5000msec;and D: 2,4,8,16,24,34,50msec).The complete cycle was repeated 3 times in each patient.
With P:500,only 2/20 T were terminated,but with P:1000, 16/20 were terminated.All T were terminated with P:5000. The only combination successful in all patients was P:5000 and D:16.No unwanted arrhythmias were induced,but in the same group rapid atrial pacing induced atrial flutter in 4 patients,being successful in the remainder.
Scans of 1 or 2 atrial or ventricular premature stimuli were successful in 18/20.The system tends to avoid stimulation in the vulnerable period,but allows stimulation in different phases of the T cycle,increasing the likelihood of safe termination.This pacemaker is capable of development into an inplantable form.

THE USE OF STIMULUS-T INTERVAL TO DETERMINE CARDIAC PACING RATE

Anthony F. Rickards, MRCP,; John Norman, The National Heart Hospital, London, U.K.

The relationship between QT interval and heart rate has been studied in a group of patients undergoing physiological exercise (N=25), atrial pacing without exercise (N=15) and in a group with complete heart block exercising at a fixed ventricular rate controlled by cardiac pacing (N=9). Total QT interval decrease for a predicted increase in heart rate of 100 bpm due to physiological exercise was 187ms, whereas for a similar heart rate increase induced by atrial pacing, the QT decrease was only 66ms. The dichotomy is explained when observations on patients exercising at a fixed ventricular rate show a QT interval decrease of 95 ms for a predicted 100 bpm increase in the independent atrial rate. Thus QT interval is not only a function of intrinsic heart rate, but also of the levels of circulating catecholamines which independently affect repolarisation time.
A cardiac pacemaker using a unipolar ventricular lead has been constructed which senses the interval between the delivered stimulus and the evoked ventricular T wave and sets the subsequent escape interval and thus the overall pacing rate. Physiological control of cardiac pacing rate is therefore possible, independent of atrial activity, using a unipolar ventricular lead.

NON-INVASIVE EVALUATION OF CEREBRAL BLOOD FLOW DURING VENTRICULAR AND A-V SEQUENTIAL PACING

Murray Miller, M.D., Stewart Fox, M.D., Russell Jenkins, M.D., Jon Schwartz, M.D., F. Geoffrey Toonder, M.D., Quakertown Hospital, Quakertown, PA

Over the last 20 years, transvenous ventricular pulse generators (VVI) have become the accepted method for permanent pacing because most patients requiring pacemakers were improved by the VVI. However, some patients do not tolerate the loss of atrial kick which accompanies ventricular pacemaker insertion, and subsequently develop decreased cardiac output and decreased cerebral blood flow. They manifest the cerebral symptoms of lightheadedness, vertigo, and syncope, now recognized as "pacemaker syndrome". Until now, the only way to prevent this syndrome was to recognize the susceptible patient in advance of pacemaker insertion by utilizing a variety of invasive, expensive, and sometimes dangerous testing techniques. We have taken proven, existing equipment and developed an accurate, reproducible, non-invasive testing technique using the OPG-GEE during pacemaker implantation to demonstrate the relative changes in cerebral blood flow during temporary ventricular pacing. These tests enabled us to recognize significant decreases in relative cerebral blood flow in 15 patients. In 14 of these patients, we proceeded to insert an additional atrial electrode and an A-V sequential pulse generator, thus preventing pacemaker syndrome. The one patient not receiving an A-V sequential pacemaker did develop pacemaker syndrome, which resolved upon a subsequent change to an A-V sequential pacemaker system. This newly developed testing technique has broadened our recognition that many more patients would benefit from physiologic pacing to prevent a decrease in cerebral blood flow that frequently accompanies VVI pacing.

TUESDAY, MARCH 17, 1981
PM
METABOLIC ASPECTS OF ACUTE MYOCARDIAL INFARCTION IN THE EXPERIMENTAL MODEL
2:00-3:30

NON-UNIFORM EFFECTS OF SYMPATHETIC NERVE STIMULATION ON VENTRICULAR REFRACTORINESS IN HEALED MYOCARDIAL INFARCTION: COMPARISON TO ACUTE INFARCTION. Marion S. Gaide, PhD; Robert J. Myerburg, MD, FACC; Henry Gelband, MD, FACC; Augustin Castellanos, MD, FACC; Arthur L. Bassett, PhD, University of Miami School of Medicine, Miami, Florida 33101.

Spontaneous arrhythmias occur in cats studied 1-12 months after healing of myocardial infarction (MI) induced by distal coronary ligation. To evaluate the interaction between the sympathetic nervous system and healed MI, we measured local ventricular refractory periods (RP) from the epicardium overlying the MI (I), the border area (B) and a normal area (N), with and without sympathetic nerve stimulation. Atrial and ventricular pacing leads and 3 bipolar test leads (N, B and I) were implanted epicardially in cats (n=6) 2-6 months after induction of MI. The SA node was crushed and right atrium and ventricle were paced 20-30 beats per minute faster than intrinsic rate. RP measurements were made after vagotomy and prior to, during and after bilateral stimulation of ansa subclavia (all proximal connections to the stellates were severed). Sympathetic nerve stimulation induced RP shortening which was greatest in N (-18 ± 2 msec), slightly less in B (-15 ± 3 msec) and least in I (-9 ± 1 msec). In contrast, sympathetic stimulation of similar zones in cats (n=6) before and 60 minutes after induction of an acute MI shortened RP uniformly in N, B and I. We conclude that experimental healed MI alters the effect of epicardial sympathetic nerves on RP, resulting in non-uniform changes in ventricular RP during stimulation. Imbalance of sympathetic outflow, or of ventricular muscle responsiveness to stimulation, may contribute to ventricular arrhythmias in hearts with healed MI.

METABOLIC CHARACTERIZATION OF REVERSIBLE VERSUS IRREVERSIBLE ISCHEMIC DAMAGE
Shukri Khuri, MD; Stephanie Karaffa, B.Sc.; Robert Kloner, MD, Ph.D.; Edward Folland, MD, FACC; Alfred Parisi, MD, FACC; Paul Moynihan, B.Sc. and Ernest M. Barsamian, MD, Harvard Medical School, Boston, Massachusetts

This study was conducted to identify metabolic criteria which would enable the intraoperative differentiation between normal, ischemic (reversible) and infarcted (irreversible) myocardial segments. In 12 open chest dogs, 8 mass spectrometer probes for the determination of intramyocardial oxygen ($Pm0_2$) and carbon dioxide ($PmC0_2$) tensions were placed in infarcted segments (In) of the left ventricular wall (created two years previously by high ligation of the anterior descending coronary artery and documented by angiography and post mortem histology), 8 in normal segments (N), and 8 in ischemic segments (Is) supplied by a critically stenotic circumflex coronary artery. Baseline gas tensions (mean±SEM) and their response to atrial pacing (30% increase in heart rate) were:

	$PmCO_2$ (mmHg)			$Pm0_2$ (mmHg)		
	N	Is	In	N	Is	In
Before pacing	45±5	62±4]*	44±4	16±3	8±2]*	18±3
During pacing	48±5	89±9]*	44±4	14±3	3±1]*	14±3

*P < 0.01

Baseline gas tensions were similar in the normal and infarcted segments, but significantly different in the ischemic segments (P<0.01). Atrial pacing elicited significant changes in the ischemic segments but not in normal and infarcted segments. These data indicate that changes in $Pm0_2$ and $PmC0_2$ in response to atrial pacing enable the identification of viable ischemic myocardial segments which would benefit from revascularization, and therefore differentiating them from normal and non-viable segments which do not benefit from revascularization.

EFFECTS OF FLUOROCARBONS AND SUPPLEMENTAL OXYGEN ON ACUTE MYOCARDIAL ISCHEMIA ASSESSED BY INTRAMYOCARDIAL GAS TENSION MEASUREMENT
Robert E. Rude, M.D.; Dietmar H. Glogar, M.D.; Shukri F. Khuri, M.D.; Stephanie Karaffa, B.S.; Robert A. Kloner, M.D., Ph.D.; Leland C. Clark, Jr., Ph.D.; James E. Muller, M.D.; Eugene Braunwald, M.D., FACC; Harvard Med. School/Peter B. Brigham Hosp. Boston, MA

Although fluorocarbons (FC), 0_2 carrying compounds which are effective as blood substitutes, have been shown to reduce myocardial infarct size, it is unknown whether they have a beneficial effect on myocardial gas tensions. We studied 27 open-chest dogs undergoing 2 sequential 5 min left anterior descending coronary occlusions (CAO) 75 min apart. 14 dogs were ventilated with 20% 0_2; after a control CAO, 7 of these dogs (Group A) received FC (40ml/kg) intravenously and 7 dogs received an equal volume of normal saline (NS) 60 min before CAO II. 13 dogs were ventilated with 100% 0_2; 7 of these dogs (Group C) received FC (40ml/kg) and 6 dogs NS before CAO II. Myocardial gas tensions were measured by mass spectrometry: $\Delta PmCO_2$ (mmHg) = rise in ischemic zone pCO_2 with 5 min CAO; $Pm0_2$ (mmHg) = ischemic zone $p0_2$ at the end of 5 min CAO. FC alone (Group A) led to a smaller rise in ischemic $pC0_2$ ($\Delta PmC0_2$ 21±5 during CAO I vs 15±2 during CAO II; $p < 0.05$) but did not effect $pm0_2$, while NS alone (Group B) had no effect. FC and 0_2 (Group C) led to both a smaller $\Delta PmC0_2$ (33±5 during CAO I vs 23±4 during CAO II $p < 0.05$) and a higher ischemic $Pm0_2$ (9±4 at the end of CAO I vs 22±7 in CAO II, $p < 0.05$), while NS + 0_2 (Group D) had no effect. We conclude that treatment with FC reduces acute ischemic injury with and without supplemental 0_2 ventilation. FC and 0_2 act synergistically; in combination they lead to increased $Pm0_2$ in the ischemic myocardium. Although numerous interventions have been shown to reduce myocardial tissue $\Delta PmC0_2$, this is the first intervention from our laboratory to improve myocardial $Pm0_2$.

HYPOTHERMIC RETROPERFUSION TREATMENT OF ACUTE MYOCARDIAL ISCHEMIA: EFFECTS ON CARDIAC FUNCTION AND INFARCT SIZE
Roberto Haendchen, MD; Noboru Aosaki, MD; Takahisa Uchiyama, MD; Xavier Escudero; Jeffrey Broffman, BA; Samuel Meerbaum, PhD, FACC; Eliot Corday, MD, FACC, Cedars-Sinai Medical Center, Los Angeles, California

To extend the viability of acutely ischemic myocardium, moderate hypothermia (H) was administered via the great cardiac vein along with diastolic retroperfusion in closed chest dogs with 6 hours occlusion of the proximal LAD coronary artery. Of 12 dogs, 6 served as untreated controls and 6 had H initiated 30 min postocclusion. Hemodynamics were monitored, cardiac function measured by two-dimensional echocardiography and myocardial necrosis evaluated by triphenyl-tetrazolium-chloride. Retroinfusate temperature was 18.7±.8°C. H treatment between 30 min and 6 hrs caused a significant ($p<.02$) drop in heart rate (from 104±10.7 to 91±9.1/min) and rate-pressure product (from 11298±680 to 7507±1526 mm Hg/min). LV stroke volume and systemic vascular resistance did not change significantly. No arrhythmias were encountered. Data on % change in LV ejection fraction (EF) from 30 min to 6 hrs and infarct size (% of LV) are listed (p values vs controls).

	Change in LV EF	Infarct Size
CONTROL DOGS	-16.0±27.9%	21.1±4.8%
H-TREATED DOGS	+32.4±5.8% (p<.01)	3.5±3.6% (p<.001)

Echo analysis of the LV section indicated a 27.2±29.7% increase in systolic percent area change during H compared to a 62.3±4.3% decrease during the equivalent period in control dogs ($p<.01$). CONCLUSION: During a 6-hr coronary occlusion in closed chest dogs, moderately hypothermic retroperfusion significantly extended myocardial viability and improved global as well as regional LV function. Retrograde delivery of hypothermia may be a safe and effective technique for treating acutely ischemic myocardium.

MECHANISM OF LOW OUTPUT IN EXPERIMENTAL RIGHT VENTRICULAR INFARCTION. James A. Goldstein, MD, Gus J. Vlahakes, MD, Edward D. Verrier, MD, Nelson Schiller, MD, FACC, John V. Tyberg, MD, PhD, FACC, Kanu Chatterjee, MD, FRCP, FACC. Cardiovascular Res. Inst., Univ. of Calif., San Francisco.

RV infarction (RVI) can result in decreased CO. To elucidate the mechanism involved, selective RVI was produced in 15 dogs with the pericardium intact. CO, intrapericardial pressure (IPP) and RV and LV pressures were measured; stroke work (SW) and end-diastolic transmural pressures (TM) were calculated. Data were obtained before (Control) and after RVI and after subsequent pericardiotomy.

mean ± SEM	Control	RVI	Pericardiotomy
CO ($L \cdot min^{-1}$)	2.0±0.6	†1.3±0.5	‡1.8±0.5
RV SW ($g \cdot m \cdot m^{-2}$)	5.3±2.7	†2.1±1.5	3.3±1.1
RV TM (mm Hg)	1.0±1.3	*1.7±1.8	††6.2±1.6
LV SW ($g \cdot m \cdot m^{-2}$)	25.9±10.1	†11.8±6.8	**21.2±6.0
LV TM (mm Hg)	4.6±1.8	†2.0±1.9	††9.2±2.8
IPP (mm Hg)	4.7±1.5	†7.6±1.8	††0±0

Analysis of variance: Control vs RVI: *P<0.05, †P<0.001; Pericardiotomy vs RVI: ‡P<0.05, **P<0.005, ††P<0.001.

RVI resulted in RV failure as evidenced by decreased RV SW despite increased RV TM; LV SW decreased concomitantly with reduced LV TM, suggesting that low CO resulted from reduced LV preload. Two-dimensional echocardiography demonstrated marked RV dilatation and decreased LV size. IPP increased and equalization of ventricular diastolic pressures was noted. Subsequent pericardiotomy increased LV SW, LV TM, CO, and RV TM, with resolution of ventricular diastolic pressure equalization.

Low CO in RVI is due primarily to reduced LV preload resulting, in part, from depressed RV function. Elevated IPP, resulting from RV dilatation, further reduced LV preload and produced diastolic pressure equalization. Pericardiotomy improved LV filling and hence increased CO. The pericardium may thus play an important role in the pathophysiology of low CO in RVI.

EARLY AND LATE PROTEOLYSIS IN ACUTE MYOCARDIAL INFARCTION Roberto Bolli, MD, Richard O. Cannon, MD, Robert E. Goldstein, MD, FACC, Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

Lysosomal proteases have been thought to play an important role both in the production and in the healing of acute myocardial infarction (AMI). However, the changes in proteolysis (PR) occurring in the evolution of AMI are unknown. Thus, control (C) rats underwent coronary artery occlusion (O); 2,6,24,48 and 72 hrs after O, slices were obtained from ischemic (IZ), normal (NZ) or border zone (BZ) myocardium and incubated for 1 hr in oxygenated or in anoxic Krebs-Ringer-HCO_3^- buffer. Cycloheximide was added (.5mM) to block protein synthesis. PR was measured by net tyrosine production (pmol/mg tissue, mean ±SE):

	2hrs(n=17)	6hrs(n=7)	24hrs(n=9)	48hrs(n=8)	72hrs(n=21)
NZ	92±13	-	86±11	102±16	114±8
BZ	-	-	192±31	401±46*	394±27*
IZ	77±7	33±11**	98±11***	262±23***	249±23***

(*=p<.02 vs 24hrs;**=p<.01 vs 2hrs;***=p<.001 vs 6 hrs) Thus, in AMI, PR follows a biphasic pattern: it decreases early, when irreversible damage develops, and later increases markedly both in the BZ and in the IZ, concomitant with the infiltration of inflammatory cells. To test the concept that this late rise in PR could be important in the healing of AMI, we gave methylprednisolone 50 mg/kg i.v. to 6 rats at 5 min after O and 50 mg/kg i.m. at 3,6,24 and 48 hrs after O: at 72 hrs PR both in BZ (225±56) and IZ (170±17) was significantly decreased (p< .02) relative to C. This inhibition of late PR may contribute to impaired healing of AMI reported when this steroid dose is given to rats. Our data suggest that lysosomal and, more generally, cellular proteases do not contribute to ischemic cell death but may play an important role in the healing phase of AMI.

TUESDAY, MARCH 17, 1981
PM
PHARMACOLOGY: CONCEPTS IN THERAPY OF VENTRICULAR ARRHYTHMIAS
4:00-5:30

CHRONIC INTRAVENOUS INFUSION OF ANTIARRHYTHMIC DRUGS USING A TOTALLY IMPLANTED DRUG DELIVERY SYSTEM
Jeffrey L. Anderson, MD, FACC; Richard P. Donahue, BS; Marilyn E. Conlon, MA; Stanislaw Pasyk, MD; Phillip L. Stetson, PhD, MD; Arthur B. Simon, MD; William E. Burmeister, PhD; Elton M. Tucker, BS; Bertram Pitt, MD, FACC. University of Michigan, Ann Arbor, MI.

The success of antiarrhythmic therapy is in part limited by an inability to maintain therapeutic steady state plasma concentrations (Css) over time. A totally implantable, self-powered drug delivery system ("Infusaid", Metal Bellows Co., Sharon, MA) has recently become available. In order to establish the feasibility of this system to chronically deliver therapeutic doses of selected antiarrhythmic agents, we subjected it to both in vitro and in vivo testing. The Infusaid pump consists of a hollow titanium disk separated into 2 chambers by a bellows and powered by pressure of fluorocarbon vapor at 37°C. Pressure on the bellows forces infusate from the reservoir (35 or 50ml) at a constant rate through a filter and fine-bore silastic catheter positioned in the vena cava. During 3 months in vitro testing, procainamide (P), and bretylium (B), were found suitable for chronic delivery. Delivery of lidocaine (35%,70%) was limited by high viscosity and corrosion of steel elements. In vivo feasibility studies in dogs lasting 2 weeks were carried out with P and B. The pump was placed in a subcutaneous abdominal pocket in 4 animals. P (0.5 g/ml), delivered at 4 ml/d (70 mg/kg/d), provided mean Css of 5.3 mcg/ml. Css was attained by 8-24 hr. B (50 mg/ml), delivered at 8 ml/d (13 mg/kg/d), provided Css of 0.80 mcg/ml (range 0.41-1.49 mcg/ml). Css was attained by 24-48 hr. In contrast, oral B resulted in mean Css of only 0.19 mcg/ml in patients. In conclusion, chronic intravenous delivery of therapeutic B and P is feasible and suggests further study in man.

EFFECT OF PROSTACYCLIN ON VENTRICULAR ARRHYTHMIAS AND INTRACARDIAC CONDUCTION IN MYOCARDIAL ISCHEMIA
Thomas L. DeBauche, M.D., Tedd A. Brandon, B.S., Lair G.T. Ribeiro, M.D., Kevin Holyfield, Richard R. Miller, M.D., FACC, Baylor College of Medicine, Houston, Texas

Several of the prostaglandins have been shown to possess antiarrhythmic properties. To elucidate the effects of prostacyclin (PGI_2) on ventricular (V) ectopy in acute ischemia, 29 dogs undergoing proximal left anterior descending coronary artery occlusion (CAO) were randomized to PGI_2 (n=12) or control (C) (n=17). Occlusion site was equal (p=ns) in both groups. All had continuous ECG recordings and 11, His bundle electrography. PGI_2, .5-2.0 µg/kg/min began 15 min pre-CAO and continued 30 min post-CAO. Post-CAO, V ectopic beats per 1000 beats were reduced by PGI_2: C, 160±49; PGI_2, 63±27, (-60%; p<.02). V tachycardia (tach) episodes were similar: C, 24 in 17 dogs; PGI_2, 14 in 12 dogs (p=ns). However, in C, V tach resulted in V fibrillation in nine animals (53%) vs one (8%) in PGI_2 (p<.02). V tach features were examined: duration, C, 14±14 (SD) beats vs PGI_2, 6±10 (p=ns); cycle length, C, 203±49 msec vs PGI_2, 317±75 (p<.02). PGI_2 did not alter sinus rate (153±8 to 149±9 bpm) or HV intervals (36±2 to 35±2 msec) (both p=ns); AH was shortened 79±5 to 70±6 msec (p<.05). In eight dogs given a nitrate to lower BP equal to PGI_2, AH was unchanged. Thus, PGI_2 reduces total ventricular ectopy and tends to shorten AH conduction in acute myocardial ischemia. Of particular interest, PGI_2, while not preventing the occurrence of ventricular tachycardia, increases the V tach cycle length and attenuates the progression to ventricular fibrillation. Thus, PGI_2, in acute myocardial ischemia, markedly reduces the occurrence of ventricular fibrillation and mortality during the first 30 minutes following coronary artery occlusion.

MEXILETINE FOR RESISTANT VENTRICULAR TACHYCARDIA: COMPARISON WITH LIDOCAINE AND ENHANCEMENT OF EFFICACY BY COMBINATION WITH QUINIDINE. Henry J. Duff, M.D., Dan M. Roden, M.D., R. Kirby Primm, M.D., Edmund L. Carey, M.D., John A. Oates, M.D. and Raymond L. Woosley, M.D., Ph.D. Departments of Pharmacology and Medicine, Vanderbilt University School of Medicine, Nashville, TN.

Mexiletine (Mex) is a structural analog of lidocaine (Lid) with antiarrhythmic (AA) activity when given orally. We studied 12 patients (pts) with recurrent ventricular tachycardia (VT) nonresponsive (NR) to all conventional oral agents, assessing 1) the degree of correlation between response (R) to Lid and R to oral therapy with Mex, and 2) the R to quinidine (Q) combined with Mex in pts resistant to Mex and Q given separately. NR was defined as persistence of VT or <70% suppression of ventricular ectopic depolarizations (VED). Of the 12 pts, 10 had ischemic heart disease, 7 had required repeated cardioversions due to VT, and the remaining 5 had symptomatic recurrent nonsustained VT. VED and VT frequency were quantitated before therapy, during infusions of Lid at plasma concentrations in the usual therapeutic range, and during trials of gradually increasing dosages of Mex. If pts were NR to Mex, Q was added. Results:

	Lid R	Lid NR	5/12 Pts NR to Mex Alone:	Mex	Mex+Q	Q
Mex R	5	2	Pts R/Pts NR	0/5	5/5	0/5
Mex NR	0	5	%↓VED($\bar{x}$±SD)	65±16	94±4	56±16

VT suppression continues during outpatient therapy for a mean of 5 months (SD=2). All pts responding to Lid responded to Mex; however, lack of R to Lid did not preclude a R to Mex in two pts. The addition of Q, a type I AA agent, enhanced the efficacy of Mex, a type II AA agent, suggesting that combination therapy with drugs having different electrophysiologic properties may improve AA efficacy.

LACK OF EFFECTIVENESS OF BRETYLIUM IN PAROXYSMAL SUSTAINED VENTRICULAR TACHYCARDIA

Robert Bauernfeind, MD, FACC; Steven Swiryn, MD, FACC; Edwin Palileo, MD; Boris Strasberg, MD; Elise Duffy, MD; Daniel Scagliotti, MD; Kenneth Rosen, MD, FACC, University of Illinois, Chicago, Illinois.

Bretylium tosylate (BRET) has been recommended for use in patients (pts) with drug-resistant ventricular tachycardia (VT) or fibrillation (VF). Programmed stimulation (PS) is a technique for evaluating prophylactic drug effectiveness in paroxysmal sustained VT. In this study, we utilize PS to evaluate BRET in 6 consecutive pts with recurrent paroxysmal sustained VT (two pts also had VF). These pts, aged 21 to 67 (mean 56) yrs, had remote infarctions (5 pts) or cardiomyopathy (1 pt). All 6 pts had inducible sustained VT during control PS. Intravenous (IV) BRET (10 mg/kg) was infused over 30 min, and PS repeated 30 min after infusion. In 5/6 pts, PS induced sustained VT of identical morphology and similar cycle length (CL) to control VT (CL 324 ± 15 with BRET vs 340 ± 17 msec in control) (NS). In 1/6 pts, VT could not be induced after IV BRET. This pt was subsequently studied on oral BRET. After 48 hours of 1.0 gm BRET q 6 hours, this pt had inducible sustained VT of identical morphology and similar CL to control VT (CL 330 with BRET vs 340 msec in control). A second oral study (48 hours of 1.6 gm q 6 hours) revealed induction of sustained VT of new morphology (CL 320 msec). All pts tolerated control VT well. Three pts tolerated BRET VT poorly (hypotension), one of these pts requiring emergent cardioversion. In conclusion, BRET had little effect on induction (and CL) of paroxysmal sustained VT. Our results imply that IV or oral BRET would be of little value in this arrhythmia, and could be deleterious because of hypotension.

PROTECTION AGAINST VENTRICULAR FIBRILLATION BY CALCIUM ANTAGONISTS. Francis T. Thandroyen, MRCP; Louise Higginson, BSc; Christian W. Hamm, MD; Lionel H. Opie, MD, FACC. MRC Ischaemic Heart Disease Research Unit, University of Cape Town, South Africa.

To investigate the possible role of calcium ions in the genesis of ventricular fibrillation, we studied the effects of verapamil, nifedipine and diltiazem on the ventricular fibrillation threshold (VFT) of isolated perfused rat hearts before and after coronary artery ligation. The highest concentration that did not cause heart block was used. Results were (Means ± SEM for 6 hearts):

	Ventricular fibrillation threshold mA			
	Pre-ligation	2 min post ligation	5 min post ligation	15 min post ligation
Control	8 ± 1	6 ± 1	3 ± 1	2 ± 0.5
Verapamil 1.5×10^{-7}M	12 ± 2	8 ± 1	7 ± 1**	5 ± 0.5**
Verapamil paced	14 ± 2*	13 ± 1**	10 ± 2**	7 ± 2*
Nifedipine 1×10^{-6}M	17 ± 4**	12 ± 2	9 ± 1***	5 ± 1***
Diltiazem 1×10^{-6}M	10 ± 2	8 ± 1	5 ± 0.5	3 ± 0.5*

*P<0.05 **P<0.02 ***P<0.001 versus control hearts

Thus verapamil and nifedipine protected against the fall in VFT almost throughout the ischemic period, while diltiazem showed protection only at 15 min. These favourable effects were not mediated by changes in coronary flow, heart rate, tissue metabolism (high energy phosphates), nor by decreased tissue cyclic AMP. We conclude that: (1) protection against VF occurred as result of inhibition of transmembrane calcium flux, and (2) that calcium ions play an important role in the genesis of VF in our model.

IMPROVED SURVIVAL IN SUDDEN DEATH/VENTRICULAR TACHYCARDIA PATIENTS WITH THERAPEUTIC ANTIARRHYTHMIC DRUG LEVELS. Stephen C. Vlay, MD; Clayton H. Kallman, Sc.M; Philip R. Reid, MD, FACC. Johns Hopkins University, Baltimore, Maryland.

Fifty six patients (pts) with hypotensive ventricular tachycardia or sudden death/ventricular fibrillation refractory to conventional drugs were treated with aprindine (Ap) until hypotensive ventricular tachycardia was abolished. Failure was defined by death or syncope. Dose adjustment of Ap was complete after an average of one month. Initial blood levels (IBL) (between day 25-50 post-entry) were available on 43 pts. Another 13 had no level during this period but did have prior and/or subsequent levels. Based on the initial blood level, pts were divided into 2 groups: Ap>1.5 ug/ml and Ap≤1.5 ug/ml. Range of deaths for the 43 pts was 62-1583 days with the median time to death 690 days for IBL>1.5 ug/ml and 251 days for IBL≤1.5 ug/ml. Kaplan Meier Survival Curves (KMSC) were plotted and tested by the generalized Wilcoxon Test for differences in survival. Survival of the IBL>1.5 ug/ml group was consistently better than the IBL≤1.5 ug/ml group ($p<.03$). To examine variability over time, average blood level (AvBl) was calculated for all 56 pts using all levels post day 26. KMSC again showed better survival for the AvBl >1.5 ug/ml group ($p<.029$). Ten known predictors of survival (sex, # infarct, congestive heart failure, angina, diabetes, hypertension, smoking, family history of sudden death, a lesion of the left anterior descending proximal to the first septal perforator, abnormal contractility in the posterobasal segment of the left ventricle) showed no difference in distribution between IBL>1.5ug/ml and IBL≤1.5 ug/ml groups. Thus improved survival was observed with therapeutic levels of Ap >1.5 ug/ml in this high risk group.

TUESDAY, MARCH 17, 1981
PM
PEDIATRIC CARDIOLOGY—CLINICAL STUDIES
4:00-5:30

COLLABORATIVE STUDY OF BLADE ATRIAL SEPTOSTOMY

Sang C. Park MD, FACC; William H. Neches MD, FACC; Charles E. Mullins MD, FACC; Robert A. Mathews MD; Frederick J. Fricker MD; Lee B. Beerman MD, Cora C. Lenox MD, FACC, J. R. Zuberbuhler MD, FACC
University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh, Pittsburgh, Pa.

During the past 3 years, 5 institutions have collaborated in an evaluation of the efficacy of blade atrial septostomy (BS). Forty-three patients underwent BS, including 25 with transposition of the great arteries (TGA), 10 with mitral atresia complex (MAC), 3 with tricuspid atresia (TAT) and 5 with miscellaneous anomalies. Ages ranged from 1 day to 12 years. Twenty-nine (67%) were under 6 months of age, 6 between 7 and 12 months and 8 were older than 1 year at the time of BS. Clinical improvement occurred in 20 of 25 (80%) patients with TGA. In 2 patients a large atrial septal defect (ASD) was created by the procedure but adequate mixing did not occur and early Mustard operation was performed. Three other patients had borderline size ASD prior to BS and the blade did not engage the interatrial septum (IAS). Seven of 10 patients with MAC had a good result with BS. In 2 patients in this group the LA was too small to permit extension of the blade. Three patients with TAT and the 5 patients in the miscellaneous group had an excellent result. Immediate improvement occurred in 81% of the 43 cases. Four patients had intact IAS and BS was successfully performed by transseptal technique. Among 17 patients who have undergone follow-up evaluation of interatrial opening (IAO) re-stenosis of the IAS was observed in 3 patients 10 to 22 months after the BS. There was a single mortality, a result of laceration of the left atrial wall. Minor complications were observed in 3 patients. BS is an effective palliative procedure, even with thickened IAS or with an intact IAS.

HEMODYNAMIC EFFECTS OF HYDRALAZINE IN INFANTS WITH LARGE VENTRICULAR SEPTAL DEFECT.

Robert H. Beekman, M.D., Albert P. Rocchini, M.D., Amnon Rosenthal, M.D., F.A.C.C., University of Michigan Medical School, C.S. Mott Children's Hospital, Ann Arbor.

To evaluate the effects of acute afterload reduction, Hydralazine (HZ, .2 mg/kg) was administered at cardiac catheterization to 6 infants with large ventricular septal defect (VSD). Age ranged from 2.5 to 11 (mean 5.3) months. Prior to HZ and 5, 15, 25, and 35 minutes after HZ the following were measured: Ao, pulmonary capillary wedge (PcW), PA, RA, SVC pressures and saturations, heart rate (HR), and oxygen consumption (VO2). Hemodynamic effects were noted 5 minutes post-HZ but were most pronounced 35 minutes post-HZ. Pre-HZ baseline data were therefore compared to 35 minute post-HZ values. Pulmonary flow (Qp) did not change while systemic flow (Qs) increased significantly (4.6 ± 0.3 to 6.6 ± 0.5 L/min/m^2, $p<.01$, mean $\pm$ SEM). The Qp/Qs ratio decreased (3.5 ± 0.4 to 2.3 ± 0.3, $p<.01$) as did the absolute left to right shunt (11.1 ± 1.5 to 8.2 ± 1.4 L/min/m^2, $p<.05$). As expected HZ caused a significant decrease in systemic resistance (Rs, 13.5 ± 0.7 to 9.6 ± 0.8 units, $p<.001$). Pulmonary resistance, PcW pressures, HR, and VO2 did not change following HZ. A small but significant decrease in RA pressure (4.2 ± 0.7 to 2.3 ± 0.7 mmHg, $p<.05$) was observed. In conclusion, HZ caused a significant increase in Qs, and a significant decrease in both Qp/Qs ratio and absolute left to right shunt in 6 infants with large VSD. These effects appear to be related to the decrease in Rs which occurred with HZ. This is in contrast to our previous work documenting hemodynamic deterioration with nitroprusside in a similar group of infants with VSD. Thus, HZ may be beneficial in the management of infants with large VSD.

SAFETY AND EFFICACY OF SHORT AND LONG TERM VERAPAMIL THERAPY IN CHILDREN WITH TACHYCARDIA

David Sapire, MD; Margo Schleman, MD; Anna O'Riordan, MD; Iain Black, MD, Temple University and St. Christopher's Hospital for Children, Philadelphia, PA and The University of Texas Medical Branch, Galveston, Texas

Seven children aged 3 months to 11 years have been treated with Verapamil (V) because of resistant, symptomatic supraventricular tachycardia (SVT), or because of complications of conventional therapy. Two of 3 patients with congenital heart disease were post-operative. The others had no gross cardiac anomalies. Three patients had SVT with WPW syndrome, 3 had ectopic SVT and 1 had atrial flutter (AF). Intravenous V was given in a dose of 0.15 to 0.25 mg/kg in 6 patients, 4 of whom converted successfully. One patient was placed on oral V only. Treatment failed in the patient with AF and one patient with WPW and a wide QRS tachycardia. Five patients were placed on continuing oral therapy. One patient died of post-operative complications while on V. Four patients have remained on oral V for 1 to 4 years at this time. The dose is 80 mg., 6 or 8 hourly depending upon response. Two of these have ectopic SVT which recurs when therapy is stopped. In the 2 with WPW and SVT, one patient has had no recurrences and in the other attacks have decreased from 1-2/week to 1-2/month. The duration of these attacks has also diminished. There have been no side effects of chronic drug administration. None of the 6 patients who received intravenous V showed any untoward effects during administration. Our experience indicates that V which so far has not been used extensively in children is an effective and safe anti-arrhythmic drug capable of controlling both ectopic and re-entrant SVT when conventional methods fail. The presence of underlying congenital heart disease should not be contraindication to its use.

CLINICAL AND ELECTROPHYSIOLOGIC PREDICTION OF NEED FOR PACEMAKER INSERTION IN CHILDREN WITH CONGENITAL COMPLETE ATRIOVENTRICULAR BLOCK

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The Lillie Frank Abercrombie Section of Pediatric Cardiology, Baylor College of Medicine, Houston

The criteria for pacemaker insertion (PM) in patients with congenital complete AV block (CCAVB) have not been defined. In an attempt to define such criteria we evaluated 22 children with CCAVB, ages 1 day-14y (median 7y) with surface ECG, treadmill exercise testing (TM) noting change in resting heart rate (HR) and prevalence of ventricular ectopy (PVC) and intracardiac electrophysiologic studies (EPS) including identification of site of block, corrected pacemaker recovery time (CPRT), and His to ventricle interval (HV). Patients were followed 1-19y (median 6y), noting age of onset of any syncopal episodes (SX). Associated congenital heart defects (CHD) were found in 5/22 children. Site of block was localized to the AV node (AVN) in 17/22, His Bundle (HB) in 3/22, below HB (BHB) in 1/22, and was unknown in 1/22 patients. Data are as follows:

	No.	BLOCK SITE			HR	CHD	SX	EPS		TM		
		AVN	HB	BHB	(Md			CPRT-msec <2000	>2000	No.	%Δ HR (mean)	PVC
PM	10	8	1	1	45	2/10	6/10	-	5/9	5/10	100	2/5
NO PM	11	9	2	-	60	3/11	1/11	2/9	2/9	6/11	130	1/6

The HV was normal in 20/20 patients. Evaluation of the 7 SX patients revealed AVN block in 6/7, 3 of whom had SX at 2y of age. The HR in all SX patients was <52BPM whereas no patient with HR>52BPM experienced syncope ($p<0.01$). CPRT estimation was performed in 4/7 SX patients; all were >2000msec. However, 3 asymptomatic patients also had CPRT>2000msec. The %Δ in HR during TM was not significantly different between sites of block. We conclude: 1. Localization of CCAVB to the AVN does not mitigate against syncope; 2. The best single predictor of SX either clinically or during EPS was a low HR; 3. EPS may be of little benefit as neither site of block nor CPRT are valid predictors of SX; 4. TM is of little benefit in predicting site of block or SX.

MULTIPLE ATRIOVENTRICULAR NODAL PATHWAYS - A NEW ELECTROPHYSIOLOGICAL PHENOMENON IN CHILDREN

Alfonso Casta, MD; Grace S. Wolff, MD, FACC; Dolores Tamer, MD, FACC; Ashok V. Mehta, MD; Otto L. Garcia, MD, FACC; Katharine G. Smith, BSN; Henry Gelband, MD, FACC, University of Miami School of Medicine, FL and University of Texas Medical Branch, Galveston, TX.

Functional longitudinal dissociation of the atrioventricular node into multiple pathways has been demonstrated in adults with reentrant supraventricular tachycardia. Atrial extrastimulus (AES) technique disclosed multiple pathways in 4 children with heart disease; none had dysrhythmias. AES were coupled to sinus and paced rhythms until atrioventricular nodal effective and functional refractory periods were reached. Multiple pathways were identified by sudden increases in atrioventricular conduction which resulted in discontinuous atrioventricular nodal curves in these children. Four pathways were shown in one patient during AES coupled to sinus; and 3 during AES coupled to paced rhythms. Three pathways were shown in 2 patients during AES coupled to sinus; and 2 pathways during AES coupled to paced rhythms. Three pathways were shown in 1 patient during AES coupled to paced rhythms; and none during sinus. The effective refractory period of the fastest pathways ranged between 290 and 455 msec; functional refractory periods between 340-520 msec. The effective refractory periods of the slower pathway ranged between 260-360 msec; functional refractory periods between 400-665 msec. Atrial echoes or supraventricular tachycardias were not induced. In conclusion, despite the foundation for supraventricular tachycardia and contrary to the adult patient, multiple pathways may be only a curious finding in children since dysrhythmias could not be induced nor clinically observed.

TUESDAY, MARCH 17, 1981
PM
SURGERY FOR ACQUIRED VALVULAR HEART DISEASE
4:00-5:30

HEMODYNAMIC RESULTS FOLLOWING AORTIC VALVE REPLACEMENT WITH THE HANCOCK STANDARD ORIFICE BIOPROSTHESIS

A. Michael Borkon, M.D., Charles L. McIntosh, M.D., Michael Jones, M.D., Lewis C. Lipson, M.D., Kenneth M. Kent, M.D. and Andrew G. Morrow, M.D., Clinic of Surgery, National Heart Institute, Bethesda, Maryland

In order to improve hemodynamic results, aortic annulus enlargement has been recommended as an adjunct to valve replacement with the Hancock bioprosthesis. In order to determine a need for this additional procedure, postoperative cardiac catheterization data from 73 patients were reviewed. All patients underwent aortic valve replacement with Hancock standard orifice bioprostheses; annulus enlargement was not employed. Postoperatively, all but 2 patients were NYHA Class I or II. Peak systolic gradient (PSG), cardiac index (CI), body surface area (BSA), and effective valve orifice area (EOA) were determined. Resting data, mean ± SEM, were:

Size	No⁰	BSA(M^2)	PSG (mm Hg)	EOA (Cm^2)
21	15	1.63±0.03*	10±3†	1.27±0.17#
23	25	1.83±0.04	7±2	1.46±0.11
25	20	1.92±0.04	7±2	1.72±0.20
27	13	1.92±0.05	5±3	1.97±0.06

*=p<0.001 21 vs 23,25,27, †=N.S., #=p<0.05 21 vs 25,27

CI (2.6 ± 0.1 L/min/m^2) and EOA index (0.86±0.05 Cm^2/m^2) were similar for all sizes. Isoproterenol infusion (15 pts) increased PSG to a mean of 44 mm Hg (range 10-85) independent of valve size. Residual PSG or small EOA did not preclude satisfactory clinical improvement. Small diameter Hancock bioprostheses demonstrate acceptable clinical and hemodynamic function when limited to patients with small BSA. In these instances annulus enlargement is rarely necessary.

THE EFFECT OF AGE AND CYANOSIS ON THE PROTEIN BINDING OF QUINIDINE IN THE PEDIATRIC PATIENT.

Arthur S. Pickoff, MD, Kenneth M. Kessler, MD, FACC, Grace S. Wolff, MD, FACC Dolores F. Tamer, MD, FACC, Otto L. Garcia, MD, FACC, Henry Gelband, MD, FACC. Department of Pediatrics and Medicine, University of Miami School of Medicine, Miami, Florida.

Quinidine (Q), an antiarrhythmic agent utilized to treat arrhythmias in the pediatric age group, has been shown to be highly bound to serum protein in the normal adult patient (pt)(unbound drug = 10% of total serum Q). Since only the unbound Q is free to act upon the myocardium, as well as at sites of metabolism and excretion, differences in the protein binding of Q in the pediatric pt could result in alterations of the clinical pharmacology of Q. In order to study the protein binding of Q in children, serum samples were obtained from 6 normal newborn infants (Group I), 6 infants ages 8-18 months (Group II), 10 pts with acyanotic congenital heart disease (CHD) ages 2-11 years (Group III) and 5 pts with cyanotic CHD ages 9-19 years (Group IV). Quinidine (2 mcg/ml) was added to the pt's serum and an ultrafiltrate obtained. The ratio of Q in ultrafiltrate to serum was determined by spectrofluorophotometry and used to calculate % free Q. The % free Q in Group I was 39.2 ± 10.8; Group II 21.3 ± 7.4 and Group III 14.2 ± 5.4, demonstrating increased protein binding with age ($p < .001$). The pts with cyanotic CHD (Group IV) had significantly greater % free Q than pts with acyanotic CHD (Group IV)(33.7 ± 12.8 vs 14.2 ± 5.4, $p < .001$). We conclude that the protein binding of Q is diminished in the young pediatric pt as well as in pts with cyanotic CHD and that this may result in alterations of Q pharmacokinetics and pharmacodynamics in these patients.

CALCIFICATION OF CARDIAC VALVE BIOPROSTHESES: HISTOLOGIC, ULTRASTRUCTURAL, AND BIOCHEMICAL STUDIES IN A SUBCUTANEOUS IMPLANTATION MODEL SYSTEM.

Michael C Fishbein, MD, FACC, Robert J Levy, MD, Aws Nashef PhD, Victor J Ferrans, MD, PhD, FACC, Lyle C Dearden, PhD, Arden P Goodman, Alain Carpentier, MD, PhD. Cedars-Sinai Med Ctr, L.A., CA, Children's Hosp Med Ctr, Boston, MA, Amer Edwards Labs, Santa Ana, CA, and Hosp Broussais, Paris, France.

To study the process of calcification(Calc) in bioprostheses, 120 glutaraldehyde-treated porcine aortic valve leaflets(PVLs) were implanted subcutaneously in rabbits and removed 1 day to 6 months(mo) later; morphologic findings were correlated with biochemically determined levels of calcium(Ca++) and γ-carboxyglutamic acid (Gla), a vitamin K dependent Ca++ binding amino acid known to be present in tissues with pathologic Calc. In PVLs explanted from day 1 to 7, which showed only inflammatory infiltrates, Ca++=382-465, and Gla=.32-.56 (these and all subsequent values in nm/mg protein). In PVLs explanted at 1-1.5 mo, Calc of PVLs and degeneration of collagen were noted histologically and ultrastructurally, and increased with time as did Ca++ and Gla levels; at 5-6 mo Ca++=7300-8060 and Gla=2.0-3.1. In PVLs implanted in patients 22 to 64 mo, Ca++=7527-30441 and Gla= 4.3-18.3. Ca++/Gla molar ratios in PVLs from this experimental system explanted at 5-6 mo also were comparable to those in clinical specimens explanted from 22 to 64 mo. In conclusion, in this experimental system, structural and biochemical alterations, particularly those related to Calc, are similar to those observed in PVLs explanted from patients, but occur much sooner. As with pathologic Calc of other tissues, progressive Calc was accompanied by increased Gla levels, suggesting that Gla plays an important role in Calc of PVLs. This model allows rapid comparative evaluation of large numbers of PVLs maintained under identical host conditions.

EXPERIENCE WITH PRIMARY FAILURE OF PORCINE BIOPROSTHETIC CARDIAC VALVES

Donald J Magilligan,Jr MD, Steven Palmisano,David Smith, BS, Paul Stein,MD, Henry Ford Hospital, Detroit, Mi

Follow up on 587 porcine bioprosthetic cardiac valves inserted from October 1971 to June 1980 was completed with only four patients lost to follow up. Primary valve failure occurred in 27 valves. Primary failure was defined as valvular stenosis or insufficiency documented by tissue degeneration in the explanted valve without histologic or bacteriologic evidence of infection. The incidence of primary failure was:at five years - 4%±1.2 S.D.; at six years - 7%±1.8, at seven years - 13%±2.5, at eight years - 19%±4.1 and at eight and one-half years - 25%±7.1. There was no significant difference in primary failure between the aortic or mitral position, male or female, patients anticoagulated or not,or valves rinsed in antibiotics or not.At eight years the failure rate in patients ≥ 35 years (10%±2.7 S.D.) was significantly less than in patients < 35 years (61%±15) (p=0.0003).Analysis of valve position with respect to age showed that mitral valves in patients < 35 years had a significantly higher rate of failure (70%±17) than mitral valves in patients ≥ 35 (9% ±3) or than aortic valves in either age group (13%&11%) (p=0.0005). Echocardiography showed cusp thickening with duration of implantation and prior to tissue failure. Phonocardiography showed the dominant frequency of the bioprosthetic sound became higher with the duration of implantation and mimicked native valve stenosis suggesting progressive cusp stiffening. Eight and one-half year experience with porcine bioprosthetic valves shows primary failure occurs mainly in the mitral position in patients < 35 years. Specific factors leading to failure in these patients and to sporadic failure in others requires further investigation.

ECHOCARDIOGRAPHIC ASSESSMENT OF THE ST. JUDE MITRAL PROSTHESIS.

Martin St. John Sutton, MD, Raymond Roudaut, MD, Paul Oldershaw, MD, Nathaniel Reichek, MD, Derek Gibson, MD, Hospital of the University of Pennsylvania, PA

The ideal mitral prosthesis is 1) non-obstructive, 2) non-thrombogenic and, 3) durable. Since only long-term follow-up will provide answers to 2 and 3, regarding the St. Jude prosthesis, we assessed 1 by determining the effects of this all-pyrolite carbon valve upon LV filling characteristics. We measured the peak rates of increase in LV dimension, (peak filling rate), and the duration of the rapid diastolic filling period using computer-assisted analysis of the LV echograms in 27 patients with St. Jude mitral valves. To elucidate how obstructive the St. Jude valve was compared to other prostheses, we contrasted the results with similar data obtained from 30 patients with Starr-Edwards(SE), 30 with Bjork-Shiley(BjS) mitral valves, and 20 normal subjects. All patients were operated upon for either rheumatic or degenerative mitral valve disease. Echoes were obtained 3 months postop.

	Normal (20)	St.J (27)	BjS (30)	SE (30)
Peak LV filling rate.(cm/sec)	14.5±2.3	13.2±3.4	105±4.2	7.4±3.0
Rapid filling period.(ms)	160±50	165±45	180±80	295±110

Peak LV filling rates in patients with St. J. valves were normal and significantly greater than in those with SE($p<.001$) or BjS ($p<.02$) prostheses. However, the duration of the rapid filling period was similar in patients with St. J and BjS valves, but significantly shorter than in those with SE valves. We conclude that 1) in patients with St. J valves LV filling was similar to normal, 2) the St. J. was significantly less obstructive to LV filling than the SE or BjS, due to its low profile, 90° leaflet opening angle, and its maximal orifice to valve diameter.

LONG TERM RESULTS OF TRICUSPID VALVE REPLACEMENT - THE PROBLEM OF LATE THROMBOSIS

John J. Morgan, F.R.A.C.P., F.A.C.C., Charles W. Thorburn, M.R.C.P., St. Vincent's Hospital, Sydney, Australia.

The occurrence of a high incidence of late thrombosis of tricuspid valve prostheses had led to a complete followup of all patients who have undergone this operation at our institution. The group of 71 patients consisted of one single, 32 double, and 37 triple valve replacements. Valve types used were : from 1966-71, 27 Starr-Edwards model 6102 (SE); from 1971-75, 32 Bjork-Shiley (BS); from 1975-76, 8 Lillehei-Kaster (LK); and from 1976-80, 10 Porcine-Heterograft valves (PX). Operative mortality was 10%. Actuarial survival at 5 years was 72%, and at 13 years, was 50%. The type of valve used, or the number of valves replaced did not alter the survival. Complications per patient year followup were : endocarditis 0.5%, embolism 3.2% (fatal 0.2%), haemorrhage 5.6% (fatal 0.7%), permanent pacing 1.5%, and tricuspid valve thrombosis (TVT) 2.2%. There were 8 with TVT in 40 patients with tilting disc valves (BS & LK) and one in 27 patients with SE valves ($P<0.05$). No PX valves thrombosed in a shorter followup. Presentation in the 9 patients was insidious, with oedema and breathlessness. There was an elevated JVP present in 9, tricuspid diastolic murmur in 8, and reduced valve sounds in 5. Thrombolytic therapy was successful in one patient and failed in a second. Reoperation was performed in 8 patients with no mortality. It is concluded that there is a continuing high morbidity and mortality with tricuspid valve replacements. Obstructing thrombosis is common with tilting disc prostheses, but not with SE valves. Reoperation can be performed at low risk.

REGURGITATION OF PROSTHETIC HEART VALVES: DEPENDENCE ON HEART RATE AND CARDIAC OUTPUT.

Kevin C. Dellsperger, David W. Wieting, Ph.D., Debra A. Baehr, Robert J. Bard, Jean P. Brugger, Earl C. Harrison, M.D., F.A.C.C., LSU School of Medicine, Shreveport, LA

Prosthetic heart valves exhibit retrograde flow and leakage; however, no well controlled study to evaluate the influence of factors such as cardiac output and heart rate has been reported to date. To evaluate these factors, four clinically used prosthetic aortic valves (size 27 mm) were studied in a pulse duplication system at heart rates of 50, 80, 110 and 140 beats/min, cardiac outputs of 2, 4, 6 and 8 L/min, mean aortic pressure of 100 mmHg, and left atrial pressure from 1 to 20 mmHg. The valves studied were the St. Jude Medical (SJM), Björk-Shiley (BS), Björk-Shiley Convexo-Concave (BSC) and the Starr-Edwards Model 1260 (SE). The total backflow for the SJM aortic valve ranged from 9.8% (110 beats/min, 8 L/min) to 34.8% (110 beats/min, 2 L/min). For the BS aortic valve the total backflow ranged from 8.9% (110 beats/min, 8 L/min) to 35.0% (80 beats/min, 2 L/min). The BSC aortic valve had a total backflow that ranged from 9.5% (110 beats/min, 8 L/min) to 33.9% (140 beats/min, 2 L/min). The total backflow for the SE aortic valve ranged from 7.3% (140 beats/min, 6 L/min) to 19.3% (140 beats/min, 2 L/min). In addition to total backflow, the regurgitation was calculated in cc/stroke. The results were as follows: for the SJM, the range of backflow in cc/stroke was 6.6 to 13.3 with a mean of 9.2 cc/stroke, the BS had a range of 5.6 to 15.2 with a mean of 9.1 cc/stroke, the BSC had a range of 6.0 to 14.0 with a mean of 8.8 cc/stroke and the SE had a range of 2.3 to 6.4 with a mean of 4.2 cc/stroke. In summary, regurgitation associated with prosthetic heart valves can present a serious problem clinically, particularly with low cardiac output and tachycardia.

TUESDAY, MARCH 17, 1981
PM
THE EFFECTS OF DRUG INTERVENTION IN ACUTE MYOCARDIAL INFARCTION IN ANIMAL MODELS
4:00-5:30

THE INFLUENCE OF NIFEDIPINE ON MYOCARDIAL BLOOD FLOW IN THE ISCHEMIC AND LATERAL BORDER ZONES

William S. Weintraub, MD; Shigehiko Hattori, MD; Jai B. Agarwal, MD; Monty M. Bodenheimer, MD, FACC; Vidya S. Banka, MD, FACC; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Phila.,Pa.

The effect of vasodilators on lateral border and ischemic zone myocardial flow (MBF) is controversial due to overlapping normal and ischemic tissue. Thus 12 dogs underwent carotid to left anterior descending (LAD) perfusion. A balloon perfusion microsphere technique was used to subtract overlapping normal zone MBF from ischemic zone MBF. Post LAD occlusion (PO), Nifedipine (Nif) was given IV 3ug/kg/min for 15 min. MBF was measured before and after Nif with microspheres. Transmural samples (5mm wide) were cut from remote normal (RNZ) and adjacent border normal (BNZ), border ischemic (BIZ), intermediate ischemic (IIZ) and central ischemic (CIZ) zones.Results: MBF in ml/g/min
*p<.05 compared to above, +p<.01 compared to left

	RNZ	BNZ	BIZ	IIZ	CIZ
PO	1.52	1.46	.490+	.217+	.172
NIF	1.95*	1.71*	.576+	.202+	.149
NZ subtracted from ischemic samples					
PO	1.52	1.41	.338+	.186+	.149
NIF	1.95*	1.71*	.324+	.132*+	.112*

Nif increased normal zone but not ischemic zone tissue MBF. After correction for overlapping normal tissue, Nif decreased IIZ and CIZ flow. In the BIZ the effect of Nif on MBF was not significant. The lateral border zone had higher MBF than ischemic zone even after correction for overlapping Nl zone tissue. Conclusions: (1) Nifedipine does not increase ischemic zone MBF (2)there is a distinct lateral border zone with intermediate MBF (3) drug effects on ischemic tissue flow cannot be assessed until corrected for overlapping normal tissue.

PROTECTION OF ISCHEMIC MYOCARDIUM BY DILTIAZEM

Christian W. Hamm*, MD; Francis T. Thandroyen, MRCP; Lionel H. Opie, MD, FACC. MRC Ischaemic Heart Disease Research Unit, University of Cape Town, South Africa and *Dept. of Cardiology, University of Hamburg, W. Germany.

We investigated the effect of a new calcium 'slow channel' blocker, Diltiazem, on the ischemic myocardium in the isolated working rat heart subjected to left main coronary artery ligation. Myocardial cellular damage was assessed by loss of lactate dehydrogenase (LDH), LV work as the sum of pressure and kinetic power, and LV efficiency as work divided by myocardial oxygen uptake (MVO_2). The results at 60 min post ligation were: (Mean ± SEM)

	Control	Diltiazem concentration $1x10^{-8}M$	$1x10^{-7}M$	$4x10^{-7}M$
	(n=12)	(n=7)	(n=13)	(n=11)
LDH (U/g/hour)	9.5±0.7	9.6±0.8	5.4±0.7***	3.8±0.7***
CO (ml/min)	21.3±2.4	19.5±1.7	32.4±3.4*	30.4±2.6*
Work (mJoules/s)	4.2±0.6	4.0±0.4	7.9±1.1**	6.9±0.7**
MVO_2 (ml/min)	89±3	92±11	105±7	104±8
Efficiency (mJ/s/ml O_2)	2.9±0.3	2.6±0.2	4.4±0.5*	4.0±0.4*

*P<0.05 **P<0.01 ***P<0.0005

Diltiazem produced a concentration dependent reduction in myocardial LDH loss and maintained better mechanical function as manifest by improved CO and LV work. Enhanced myocardial function was not associated with increased MVO_2, thus efficiency of work was augmented. These changes did not correlate with tissue content of high energy phosphate or glycogen. These results indicate that Diltiazem exerts marked protection of the ischemic myocardium and may be potentially useful in the treatment of acute myocardial ischemia.

NITROPRUSSIDE IMPROVES CORONARY PERFUSION IN REGIONAL ISCHEMIA IN CONSCIOUS DOGS WITH NORMAL AND HIGH LEFT VENTRICULAR DIASTOLIC PRESSURE.

Malavalli A. Gopal, MD, William A. Neill, MD, John Oxendine, BA, VA Medical Center, Lemuel Shattuck Hospital and Tufts Univ. Sch. of Med, Boston, MA.

To determine the effects of nitroprusside(NP) on regional ischemia, experiments were done in 6 conscious dogs with balloon-cuff occluders implanted around the left anterior descending artery (LAD). Coronary blood flow (CBF) to LAD (ischemic) and left circumflex artery (LCF, non-ischemic)regions was determined by microsphere method during 5 minute periods of LAD occlusion with and without NP infusion (mean, 0.63 mg/min). The experiment was repeated 2 days later with high LVEDP produced by Inderal, Pronestyl and volume loading. Results:

	Heart Rate	Pressures(mm/Hg) Aortic mean	LVEDP	CBF (ml/min. 100g) LAD endo	LAD epi	LCF endo	LCF epi
Normal LVEDP							
Control	86	93	1	-	-	-	-
LAD occl.	103	88	5	16	17	70	55
LAD occl.+NP	134	59	1	24	21	103	98
High LVEDP							
Control	122	116	18	-	-	-	-
LAD occl.	124	93	23	22	24	113	83
LAD occl.+NP	122	62	5	31	28	171	134

With normal or high LVEDP, LAD occlusion caused marked ischemia in the LAD region, especially in the subendocardium (endo). NP infusion increased CBF to the endo and epicardium (epi) in the ischemic region about as much as in the non-ischemic region with either normal or high LVEDP. These results in conscious dogs contradict published data showing that NP worsens regional ischemia in anesthetized open-chest dogs. If we assume maximal arteriolar dilation in the ischemic region, its increased perfusion during NP suggests that the drug dilated coronary collaterals.

DIVERGENT EFFECTS OF INOTROPIC STIMULATION ON THE MECHANICAL FUNCTION OF THE ISCHEMIC AND THE SEVERELY DEPRESSED REPERFUSED MYOCARDIUM

Jean C. Mercier, MD, Ulf Lando, MD, Katsuo Kanmatsuse, MD, Michael C. Fishbein, MD, FACC, Kenji Ninomiya, MD, Gary Totten, H.J.C. Swan, MD, Ph.D. FACC, William Ganz, MD, FACC. Div. of Cardiology, Cedars-Sinai Medical Center, Los Angeles, CA

Extensive ischemic injury causes intractable pump failure unresponsive to inotropic support. Since severe depression of contraction is known to continue for hours and days following reperfusion we studied whether inotropic support, ineffective during ischemia, could improve the function of the severely depressed reperfused myocardium. Changes in segmental contraction during occlusion of the left anterior descending coronary artery (LAD) and following its reperfusion and the effect of 10 min infusions of dopamine at 8 ug/Kg/min on these changes were studied in 29 open-chest dogs by length gauges. During LAD occlusion, dopamine intensified the abnormalities of contraction. Following reperfusion alone contractile function either failed to improve or increased to only 10% of control (5 and 9 dogs respectively with 3 hours of LAD occlusion) or to 20% (15 dogs with 30 minutes of LAD occlusion). Dopamine increased segmental contraction in the reperfused myocardium to preocclusion level, except in 5 dogs in which the myocardium beneath of the length gauge was necrotic. Activation of the reperfused viable myocardium by dopamine resulted in a significantly greater augmentation of left ventricular stroke work following reperfusion than was the case during ischemia. Thus, while dopamine worsened segmental contraction during ischemia, it improved markedly the function of the severely depressed but viable myocardium following reperfusion. These data emphasize the importance of early reperfusion in the treatment of otherwise intractable pump failure, and because rapid intracoronary thrombolysis is now feasible they are of more than academic interest.

FAILURE TO REDUCE INFARCT SIZE IN THE RAT

George A. Pantely, MD; Hugh H. Kerr, University of Oregon Health Sciences Center, Portland, Oregon.

We evaluated ibuprofen (IBU), hydrocortisone (HC), and a reduction in blood oxygen affinity (↓BOA) to determine whether they could reduce infarct size in the rat. Under ether anesthesia, the following groups had cautery ligation of the left coronary artery: IBU (n=15), 12.5 mg/kg subQ given at 5 minutes, 3 and 6 hours post-myocardial infarction (p-MI); controls (n=7) received a similar volume of saline at the same times p-MI. HC (n=20) 50 mg/kg at 5 minutes p-MI: controls (n=7) were not given anything. ↓BOA induced by exposure to 11% oxygen for 24 hours followed by room air for the two hours prior to the cautery ligation (n=7); controls were handled in a similar manner except during the 24-hour period, they were exposed to room air (n=7). Exposure to 11% oxygen increased P_{50} to 43.1 torr compared to 38.7 torr for the control group. All rats were killed 48 hours p-MI. Hearts were weighed and infarct size determined by area and circumference methods. The results were:

	INFARCT SIZE (PERCENT OF LEFT VENTRICLE)	
Group	Area Method	Circumference Method
IBU	.48 ± .04 *	.54 ± .05 *
Control	.47 ± .03	.52 ± .05
HC	.47 ± .07 *	.52 ± .06 *
Control	.46 ± .02	.52 ± .03
↓BOA	.50 ± .03 *	.57 ± .04 *
Control	.48 ± .06	.53 ± .06

Results are mean ± SD (*=P > .1 for treated vs controls). IBU, HC and ↓BOA did not reduce infarct size in the rat after cautery occlusion of the left coronary artery. Reduction of infarct size may not be possible in the rat.

CALCIUM ANTAGONISTS: THEIR EFFECTIVENESS IN DECREASING THE OCCURENCE OF VENTRICULAR FIBRILLATION AND REDUCING INFARCT SIZE AFTER A CORONARY ARTERY OCCLUSION

Duarte B.Faria,MD;Tsutomu Iwasaki,MD;Takao Endo,MD; Wai-man Cheung,MS;Lair G.T.Ribeiro,MD;Peter R.Maroko,MD, FACC,Deborah Heart & Lung Foundation,Browns Mills, N.J.

Calcium antagonists(CaAnt)are a heterogeneous group of compounds that may act favorably on coronary artery spasm, arrhythmias and protect the ischemic myocardium.Our goal was to examine the effects of 3 very potent,new and dissimilar CaAnts on infarct size(IS)and on the occurence of ventricular fibrillation(VF)after coronary artery occlusion(CAO). Thus,103 open-chest dogs with CAO were randomly assigned to control(C,n=63)or treated(T,n=40)groups which were given intravenously,Bepridil(BEP,2.5mg/kg,n=13), Nisoldipine(NIS,0.1mg/kg,n=9),and methoxy-verapamil(D600), 1.2mg/kg,n=18)starting 15 min after CAO.To determine the zone of hypoperfusion(ZH)which is the area at risk that predicts IS,highly radioactive(8mCi)^{99m}Tc-labelled microspheres(15μ)were injected into the left atrium,1 min after CAO.After 6 hrs,the hearts were excised and cut into 20-25,3mm-thick slices,incubated in triphenyltetrazolium chloride(TTC)and autoradiographed.Their planimetry rendered,respectively,the extent of IS and ZH.In the control IS/ZH(% of ZH that necrosed)was 93.2±1.6% and it was reduced to 65.1±4.8% with BEP(p<.01),to 67.9±8.0% with NIS(p<.01) and to 47.8±5.2% with D600(p<.001).Treatment reduced mean arterial pressure, in 15 min,from 98±4 to 80±3mmHg(p<.001) and heart rate from 132±5 to 119±4 beats/min(p<.001). In C,13 out of 63 dogs(21%)had VF, between 15 min and 6 hr, while none of the 40 T had VF(χ^2=9.5,p<.001).IS/ZH was 93.2±1.6% in C and 60.2±3.5% in the T group,a reduction of 35%. Thus,calcium antagonists administration reduced the extent of infarctions and prevented ventricular fibrillation,suggesting an important role for these agents in the treatment of acute infarctions.

WEDNESDAY, MARCH 18, 1981
AM
NUCLEAR CARDIOLOGY: EVALUATION OF THE PATIENT WITH ISCHEMIC HEART DISEASE
8:30-10:00

QUANTITATIVE ANALYSIS OF STRESS DISTRIBUTION AND WASHOUT OF Tl-201 MYOCARDIAL SCINTIGRAMS: SUPERIORITY OVER VISUAL ASSESSMENT FOR EVALUATION OF CORONARY ARTERY DISEASE

Jamshid Maddahi, MD; Ernest Garcia, PhD; Daniel Berman, MD FACC; Alan Waxman, MD; H.J.C. Swan, MD, FACC; and James Forrester, MD, FACC. Cedars-Sinai Med Ctr., L.A., CA.

Visual interpretation (VIS) of stress-redistribution Tl-201 scintigrams is suboptimal for evaluation of extent of coronary artery disease (CAD). Using a computer method, we have evaluated 118 patients (pts) with suspected CAD. Following development of criteria for abnormality in 31 normals (nls) and 20 CAD pts, quantitative analysis (QA) was applied prospectively to 22 nls and 45 CAD pts, of whom 41 had left anterior descending (LAD), 35 left circumflex (LCX), and 34 right coronary artery (RCA) stenosis (≥50%). Multiple view 10 minute planar Tl images were obtained 6, 40 and 240 minutes after exercise Tl injection. Circumferential profiles (CP) depicted the distribution (D) and % washout (W) of 60 6° myocardial arcs. Pt DCP's and WCP's were compared to the corresponding mean -2SD calculated from the initial 31 nls. QA was compared to consensus VIS to evaluate the sensitivity (Sn) and specificity (Sp) for overall detection of CAD and CAD in individual vessels. Results in the prospective group were as follows:

		CAD	LAD	LCX	RCA	TOTAL
QA	Sn	93%	80%*	63%*	94%*	79%*
	(Sp)	(91%)	(80%)	(90%)	(73%)	(81%)
VIS	Sn	91%	56%	34%	65%	52%
	(Sp)	(86%)	(93%)	(95%)	(86%)	(91%)

(*p<.05 QA vs VIS). QA correctly identified multi-vessel CAD in 76% pts in contrast to 47% by VIS (p<.01). Furthermore, for detection of 40 vessels with 50-75% stenosis, Sn was 70% and 35% (QA vs VIS) (p<.01). Thus, this new quantitative method is more Sn than VIS for evaluation of the extent of CAD without significant loss of Sp and is more Sn for detection of moderate stenosis.

QUANTITATION OF EXPERIMENTAL CANINE MYOCARDIAL INFARCT SIZE WITH TECHNETIUM STANNOUS PYROPHOSPHATE: A COMPARISON OF MULTIPINHOLE AND ROTATING SLANT HOLE EMISSION TOMOGRAPHY

Samuel E. Lewis, MD; Ernest M. Stokely, PhD; L. Maximillian Buja, MD, FACC; Robert W. Parkey, MD, FACC; James T. Willerson, MD, FACC, University of Texas Health Science Center, Dallas, TX.

Multipinhole (MH) and rotating slanthole (RS) tomographic estimates of myocardial infarct volume measured from 1 cm thick re-constructed slices were compared to multiview planar (2D) estimates of infarct area and to histologic measurements of infarct weight. Infarcts were produced in 21 anesthetized dogs by ligation of the proximal or mid-level branches of the LAD coronary artery. Planar, MP, and RS images were acquired concurrently 24-72 hrs postinfarction, 1-2.5 hrs following IV injection of 5-10 mCi (2.5 mg) technetium stannous pyrophosphate. Results:

DETECTION OF MYOCARDIAL INFARCTION		
21 Infarcts	14 Transmural	7 Nontransmural
1-23.0 gm,	7.1-23.0 gm,	1-9.0 gm,
mean = 10.1	mean = 12.9	mean = 4.5
2D 18/27 (85.7%)	14/14 (100%)	4/7 (57.1%)
MP 19/21 (90.5%)	14/14 (100%)	5/7 (71.4%)
RS 21/21 (100%)	14/14 (100%)	7/7 (100%)

CORRELATION WITH INFARCT WEIGHT (ALL INFARCTS)			
2D	r=0.72	y=0.34X+1.99	SE=±1.87 cm^2
MP	r=0.6	y=0.84X+2.36	SE=±6.37 cm^3
RS	r=0.89	y=0.97X+2.04	SE=±2.78 cm^3

The differences between MP and RS estimates of infarct size were significant (p<0.05). We conclude: (1) tomographic imaging may aid in detection of small infarcts and (2) RS appears to be superior to MP for infarct sizing.

CLINICAL UTILITY OF COLD PRESSOR RADIONUCLIDE VENTRICULOGRAPHY IN CORONARY ARTERY DISEASE.

Joshua Wynne, MD, FACC; B. Leonard Holman, MD, FACC; Gilbert H. Mudge, MD; Kenneth M. Borow, MD, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

To evaluate the utility of cold pressor radionuclide ventriculography (RVG) in coronary artery disease (CAD), 20 patients (15 with and 5 without CAD) underwent RVG before and during cutaneous exposure to iced water for an average of 4.8±1.1 minutes. Heart rate (64.9±10.3 to 67.7±10.6, $p<0.01$) and systolic blood pressure (117±18 to 143±30 mmHg, $p<0.0005$) rose, while left ventricular ejection fraction (LV EF) fell (59.1±16.4 to 52.1±16.5, $p<0.0025$). To establish the expected response of LV EF in normals to a pressor challenge alone, systolic blood pressure in 14 volunteers was raised with methoxamine to a level similar to that obtained during the cold pressor RVG (108±29 to 141±5 mmHg), and LV EF determined echocardiographically. LV EF declined 4±2.9%, thus establishing that LV EF might be expected to decline during the cold pressor RVG up to 10% (mean + 2 SD) merely on the basis of increased afterload, and independent of any possible effect of cold on coronary blood flow. Using the criterion of ≥10% decline in LV EF as the definition of an abnormal response, the cold pressor RVG had a sensitivity of only 33% (5/15) and a specificity of 80% (4/5) for the diagnosis of CAD. We conclude that while the cold pressor RVG may be of occasional value in patients unable to perform adequate levels of exercise, its low sensitivity suggests that it is inferior to exercise RVG or even exercise electrocardiography in the diagnosis of CAD.

THE REGIONAL EJECTION FRACTION IMAGE (REFI) - AN ACCURATE METHOD FOR THE DETECTION OF CORONARY HEART DISEASE

Hylton I. Miller, MB; Jack Baron, BSc; Shimon Braun, MD; Shlomo Laniado, MD, FACC; Tel Aviv Medical Center, Israel

Computer generated colour coded REFI's derived from ECG synchronised radionuclide cardiac blood pool imaging, using an Anger camera and a simple data processing system, were obtained in 101 patients undergoing coronary angiography, at rest and during handgrip exercise (HG). Angiographic diameter narrowing of ≥50% of 1 or more major coronary branches was considered diagnostic of CHD. A regional reduction of the colour coded REFI ≥12% during HG and regional ventricular border motion abnormalities (BMA) induced by HG was considered positive for significant CHD. 34/101 patients had normal coronary arteries (NCA), 32/67 (48%) of CHD patients had Q waves on ECG.

Results	No.	Positive HG REFI	Positive HG BMA
NCA	34	2/34 (6%)	2/34 (6%)
CHD	67	66/67 (99%)	52/67 (78%)

For detection of CHD using REFI sensitivity was 99% specificity 94% as compared to sensitivity of 78% and specificity of 94% for HG BMA. Changes in ejection fraction with HG did not allow differentiation of patients with CHD.

HG with REFI was a sufficient stress for detection of CHD. It is more sensitive than conventional assessment of BMA and may prove useful as a screening test.

COLD PRESSOR THALLIUM 201 MYOCARDIAL SCINTIGRAPHY IN DETECTION OF CORONARY ARTERY DISEASE: AN ALTERNATIVE TO EXERCISE SCINTIGRAPHY

Masood Ahmad,MD,FACC; Jerzy P. Dubiel,MD,FACC; Helmut Haibach,MD; Scott H. Goldberg; John F. Sanfelippo,MD; Richard H. Martin,MD,FACC, VA and University Hospitals, Columbia, Mo.

Thirty patients (pts) (age range 37-69 yrs) with chest pain syndromes underwent myocardial scintigraphy following injection of Thallium 201 during the standard cold pressor test (CPT). Twenty-three of 25 pts with cineangiographically confirmed coronary artery disease (CAD) developed transient perfusion deficits which normalized 4 hours later. All 5 pts without CAD (confirmed by coronary cineangiography) had normal scintigrams. In 22 pts who had previously performed a symptom-limited maximum exercise stress test, the sensitivity of exercise ECG in detecting ischemia was 88% and specificity 75% in comparison to a sensitivity of 89% and a specificity of 100% by CPT-Thallium 201 scintigraphy. Exercise Thallium 201 scintigraphy was performed in 14 pts. Eleven of 12 pts with CAD developed transient perfusion deficits following exercise and the 2 pts without CAD had normal scintigrams. Identical results were obtained by CPT-Thallium 201 scintigraphy in these 14 pts. Systolic pressure x heart rate was 103.0±17.0 at 2 minutes of CPT compared to 210.0±18.0 at peak exercise ($p<0.005$). Coronary cineangiograms obtained during CPT in 6 pts with positive exercise and CPT-Thallium 201 scintigrams did not demonstrate coronary spasm.

In conclusion, our data suggest that CPT-Thallium 201 scintigraphy is highly sensitive in detecting coronary artery disease and may be helpful in evaluating patients who are unable to perform exercise. The cause of abnormal scintigrams in patients with coronary artery disease following cold pressor test is unclear.

ACCURACY OF RADIONUCLIDE ANGIOCARDIOGRAPHY IN THE DIAGNOSIS OF CORONARY ARTERY DISEASE - A PROSPECTIVE STUDY

Erle H. Austin, M.D.; Frederick R. Cobb, M.D.; R. Edward Coleman, M.D.; Robert H. Jones, M.D., FACC, Duke University Medical Center, Durham, NC

The purpose of this investigation was to assess prospectively the accuracy of rest and exercise (R/E) radionuclide angiocardiography (RNA) in detecting coronary artery disease (CAD). By retrospective analysis of 496 patients we determined optimal RNA criteria for the presence or absence of CAD. Multivariate analysis of catheterization proven normals provided a formula to predict normal exercise ejection fraction (EF) in a given patient. The presence of CAD was indicated by one or more of the following RNA measurements: 1) rest EF <.50, 2) exercise EF .06 or more < predicted, 3) exercise increase in end-systolic volume >20 ml, 4) exercise-induced wall motion abnormality. The absence of CAD was indicated by the absence of all four criteria. These criteria were used to define a positive or negative RNA, and the diagnostic accuracy was assessed in 125 consecutive patients by comparison with coronary arteriograms. Significant CAD (>75% stenosis) was present in 70 of 86 men and in 15 of 39 women. Sensitivity (SENS), specificity (SPEC) and efficiency (EFFIC) for RNA were:

	SENS	SPEC	EFFIC
86 Men	.87	.69	.84
39 Women	.80	.50	.61
125 Patients	.86	.56	.76

We conclude that R/E RNA is sensitive and specific in men. However, poor specificity limits its value as a diagnostic tool in women.

WEDNESDAY, MARCH 18, 1981
AM
MYOCARDIAL ISCHEMIA—EXPERIMENTAL AND CLINICAL
8:30-10:00

BRIEF REPEAT PERIODS OF ISCHEMIA HAVE A CUMULATIVE EFFECT AND MAY CAUSE MYOCARDIAL NECROSIS

Kenji Ninomiya, MD; Jun Hashida, MD; Ivor Geft, MD; Enrique Chaux; William Shell, MD; Michael C. Fishbein, MD, FACC; Jacob Rit, MD; Juliana Yano; and William Ganz, MD, FACC; Divisions of Cardiology and Pathology, Cedars-Sinai Medical Center, Los Angeles, California, 90048

Myocardial ischemia of less than 18 minute duration does not cause myocardial necrosis. The purpose of this study was to determine whether brief periods of ischemia, not causing necrosis singly, may have a cumulative effect when repeated. The proximal left anterior descending coronary artery (LAD) of closed chest dogs was repeatedly occluded by inflating and deflating the balloon of a 2F catheter for periods of either 15, 10, or 5 minutes followed by 15 minutes of reperfusion. Up to 18 cycles could be completed in a dog. For study of CPK enzyme release, blood was taken from the great cardiac vein (GCV) and the aorta before and at 2.5 and 5 minute intervals during each LAD occlusion, during and 1, 5, 10, and 15 minutes after deflation. After sacrifice, the coronary arteries were examined for patency and the myocardium for presence of necrosis by the triphenyl-tetrazolium chloride method (TTC) and by histology. In 6 out of 23 dogs with 15 minute occlusions, in 4 out of 16 dogs with 10 min occlusions and in 1 out of 4 dogs with 5 min occlusions, TTC detected small but distinct areas of necrosis in the subendocardium of the LAD area. Histology was confirmatory of or compatible with necrosis. In these dogs, there were periodical releases of enzymes into the GCV, peaking immediately following reperfusion and reflecting enzyme washout. Thus, brief repeat periods of ischemia have a cumulative effect and may produce myocardial necrosis. This finding seems relevant for the clinical setting of frequent anginal episodes.

QUANTIFICATION OF REGIONAL MYOCARDIAL BLOOD CONTENT IN NORMAL, ISCHEMIC AND REPERFUSED MYOCARDIUM

Takaya Fukuyama, MD and Robert Roberts, MD, FACC, Washington University, St. Louis, Missouri

Intramyocardial hemorrhage (HEM) and the "no-reflow" limit the potential benefits of revascularization during acute myocardial infarction and may limit the beneficial effects of reperfusion from intracoronary catheter dilatation or increased flow from calcium antagonists. To characterize HEM and assess whether it plays a role in the "no-reflow" phenomenon, a method was developed to quantify regional myocardial blood content (RMBC) based on ^{51}Cr-RBC injected I.V. (200 µCi) into dogs 30 minutes prior to sacrifice. From the concentration of ^{51}Cr-activity in myocardial biopsies (4 g) and blood, we calculated RMBC and compared it to regional blood flow (RBF) using Ce-141 microspheres in 60 animals. Flow was increased with intracoronary adenosine (n=16) and decreased by coronary occlusion (n=18). In 10 animals reperfusion was performed for 30 minutes and in 10 others for 60 minutes after 5 hr of coronary occlusion. In normals (n=6) RMBC was 3.3% of wet wt. Adenosine increased RBF 400% and RMBC by 32% (3.3 and 4.4%). In ischemic tissue RMBC decreased to 0.8% of wet wt and correlated with reduced RBF (.08 ml/min/g, r=.92). In contrast, in reperfused ischemic tissue RMBC increased 150% (8.2%) indicative of HEM but RBF decreased, being inversely related (r=-.92). Hemorrhage was consistently observed after 30 minutes but "no-reflow" only after 60 minutes, thus hemorrhage preceded the reduction in perfusion ("no-reflow"). Regional blood content can be quantified with ^{51}Cr-RBC and varies directly with flow in normal and ischemic myocardium. However, HEM varied inversely with flow in reperfused ischemic areas and preceded the reduced perfusion suggesting a causal relationship. Thus, reducing HEM may also minimize the "no-reflow" and improve perfusion in the ischemic area.

QUANTIFICATION OF MYOCARDIAL FUNCTION DURING TRANSIENT CHANGES IN REGIONAL CORONARY BLOOD FLOW

Steven R. Gundry,MD, Harry W. Siepp, Rodger E. Solomon,and Michael Jones, MD, National Heart Institute, Bethesda, Md.

The effect that transient changes in regional coronary blood flow (RCBF) have on regional and global myocardial function and the electrocardiogram is unknown. We examined the quantitative effects of controlled reductions in RCBF upon regional and global LV function and the endocardial ECG and compared these with LV function during the reactive hyperemia that followed. Paired piezo-electric ultrasound crystals were implanted in the LV free wall in the distribution of the left anterior descending coronary artery (LAD) in 7 dogs. An adjustable occluder encircled the LAD; RCBF was measured distal to this with an electromagnetic flow probe. In 42 trials (6±2/dog), regional and global LV function was measured before, during, and after reductions in RCBF of 25,50,75,90,and 100%. Reductions in RCBF at all levels tested caused significant depressions in LV function which were reversed during the period of reactive hyperemia that followed. The net changes in LV function that occurred between the ischemic period and the hyperemic period appear below:

Initial Flow Reduction	25%*	50%*	75%*	90%*	100%*
Change in RCBF post ischemia (%)	+179	+226*	+260*	+274*	+240*
Change in Cardiac Output (L/min)	0.1*	0.4*	0.7*	1.0*	0.9*
Change in Systolic Shortening (mm)	0.4*	0.7*	1.4*	1.5*	1.5*
Change in d length/dt (mm/sec)	2.0	4.6*	7.6*	8.4*	8.0*
Change LVEDP (mm/Hg)	1.4*	3.2*	6.6*	7.1*	7.1*
Change LV dp/dt (mm Hg/sec)	126	228	375	385	356
Change in Endocardial ST seg. (mm)	0	0	0	0	2

*p<0.05

These results indicate that LV function is quantitatively related to changes in RCBF. Major changes in LV function may occur in response to small changes in RCBF; these changes are not reflected in ECG abnormalities.

DEMONSTRATION OF EXERCISE-INDUCED ISCHEMIA WITHOUT ANGINA IN PATIENTS WHO RECOVER FROM OUT-OF-HOSPITAL VENTRICULAR FIBRILLATION

Bimlendra Sharma, Gary Francis, Morrison Hodges, Richard Asinger. Hennepin County Medical Center and the University of Minnesota, Minneapolis, MN.

Patients (pts) who survive OHVF may relate no warning symptoms of ischemia, although myocardial ischemia is the presumed mechanism.

Regional and global left ventricular (LV) function was assessed at rest (R) and during supine submaximal exercise (Ex) in 19 pts who recovered from OHVF. OHVF pts were divided into groups who were asymptomatic (asymp, n=11) and symptomatic (symp, n=8) for a history of angina and/or myocardial infarction. All pts had significant (≥70%) 2 or 3 vessel coronary artery disease (CAD). At catheterization no pt developed angina during Ex, but 15 of 19 pts developed ST-T depression (.113±.03 mV) and 14 of 19 pts developed abnormal wall motion indicating regional myocardial ischemia. From R to Ex the symp pts increased LV end-diastolic pressure (from 20±4 to 36±4 mmHg; $p < .005$) and volume (from 98±10 to 106±10 ml/m^2; $p < .004$) without change in ejection fraction (from 45±7 to 44±6%; pNS). Asymp pts increased LV end-diastolic pressure (from 20±2 to 31±1 mmHg; $p < .001$) and volume (from 88±4 to 92±7 ml/m^2; $p < .04$) without change in ejection fraction (from 49±4 to 43±4%; pNS indicating global LV dysfunction similar to the symp pts. This study has shown that OHVF pts with CAD have evidence of ischemia during Ex even in the absence of symptoms. This painless ischemia may have a role in the genesis of OHVF in pts with CAD.

HAEMODYNAMIC MONITORING IN PAINLESS MYOCARDIAL ISCHAEMIA.
Sergio Chierchia, MD; Mauro Lazzari, MD; Attilio Maseri, MD, FACC, University of Pisa, Italy and Royal Postgraduate Medical School, London, England.

Transient asymptomatic ST or T wave changes suggestive of ischaemia are frequently observed during ECG monitoring or anginal patients. In order to investigate whether these changes are indicative of transient myocardial ischaemia occurring without anginal pain we monitored continuously ECG, left ventricular pressure and dP/dt in 12 anginal patients showing frequent transient asymptomatic ST-T changes. All data were continuously recorded on analog magnetic tape and played back, at the end of the study, to be analysed both manually and by a dedicated computer programme. We collected a total of 278 ischaemic episodes, of which only 49 were accompanied by anginal pain. ST segment elevation occurred in 66 episodes (46 asymptomatic, 20 symptomatic), and ST depression in 85 (59,26). Of the 127 episodes with T wave changes only 3 were symptomatic. A marked decrease in LV dP/dt and increase in LV end-diastolic pressure (EDP) was consistently observed during the episodes regardless of the presence of anginal pain. The decrease in LV positive dP/dt in the symptomatic and asymptomatic episodes was 370±240 mmHg/sec (mean ± SD) and 235±200 respectively ($p<0.05$). Negative dP/dt decreased by 467±227 in the symptomatic episode and by 345±232 in the asymptomatic ones ($p<0.05$). LVEDP increased by 19 + 10 mmHg in the anginal episodes and by 12±8 in the asymptomatic ($p<0.05$). Mean duration of symptomatic and asymptomatic episodes was 646±460 sec. and 335±200 respectively ($p < 0.05$). Therefore, 1) asymptomatic episodes of ST-T changes are indicative of acute myocardial ischaemia regardless of the presence of anginal pain; 2) Anginal episodes are usually of longer duration and are accompanied by a greater impairment of LV function.

WEDNESDAY, MARCH 18, 1981
AM
PEDIATRIC CARDIOLOGY—PATHOPHYSIOLOGY
8:30-10:00

MYOCARDIAL BLOOD FLOW AT REST AND DURING EXERCISE IN DOGS WITH LEFT VENTRICULAR HYPERTROPHY
Jeffrey T. Whitmer PhD, MD; Frederick W. James MD, FACC; Samuel Kaplan MD, FACC; and M. Katherine Mackzum BS; University of Cincinnati College of Medicine, Cincinnati Ohio

Significant LV hypertrophy (H) with patent coronary arteries is thought to produce global ischemia during strenuous exercise. Transmyocardial blood flow and CI were measured at rest and during exercise in dogs with chronic H due to LV outflow tract obstruction. LVH (LV + septum weight/body weight = 6.56 ± .45 gm/kg) was induced by banding the ascending aorta in 7 puppies 3-4 months of age. Seven weight and age matched dogs served as controls (C) (LV + septum weight/body weight = 4.46 ± .24 gm/kg). Thirteen to 15 months after surgery myocardial blood flow and CI were measured at rest and during two levels of steady state treadmill exercise (1st Ex, 2nd Ex) using 15 u radioactive microspheres. Mean ± SEM heart rates (HR) in beats/min, CI in cc/min/kg, and anterior left ventricular (ALV) endocardial/epicardial flow ratios (R) in C and H dogs are as follows:

	HR		CI		ALVR	
	C	H	C	H	C	H
Rest	123±4	155±15*	169±19	135±17	1.30±.06	1.28±.07
1st Ex	216±5	244±15*	337±27	356±27	1.32±.05	1.15±.06*
2nd Ex	240±7	267±11*	407±46	410±31	1.31±.05	1.14±.07*

*p < .05 for C vs H

RVR and inferior LVR were not significantly different ($p > .05$) in C and H dogs. The relative shift of myocardial blood flow away from the ALV endocardium is suggestive of regional subendocardial ischemia rather than global ischemia during exercise. We conclude that regional subendocardial ischemia is a characteristic finding in chronic LVH due to obstruction.

SYSTEMIC LUPUS ERYTHEMATOSUS AND ISCHEMIC CORONARY ARTERY DISEASE
Richard R. Liberthson, M.D., Charles Homcy, M.D., Jay Fallon, M.D., Stephen Gross, M.D. and Lawrence Miller, M.D. Massachusetts General Hospital, Boston, MA

Seven patients (pts) with systemic lupus erythematosus (SLE) diagnosed at ages 15 to 29 years who developed ischemic coronary artery disease (CAD) were reviewed to clarify the spectrum of coronary artery abnormality in SLE. The role of serial angiography in diagnosis, the efficacy of steroid therapy in suspected coronary arteritis and various therpeutic options were assessed. Two distinct patterns of coronary abnormality were identified. Four pts (ages 20,29,29,36 yrs) had coronary arteritis diagnosed in 2 by postmortem and in 2 by serial angiography. In 1 pt dramatic alterations in coronary anatomy occurred with angiographic improvement temporally related to the initiation of high dose steroid therapy. Another patient with angiographically documented coronary artery obstruction responded to a combination of anti-anginal agents and steroids. In contrast to this pattern of isolated coronary arteritis, the remaining 2 pts also had generalized panarteritis. The second group (ages 22,23, 37 yrs) had severe diffuse atherosclerotic coronary disease which was identified in 2 at postmortem and in 1 on angiography. In the latter, coronary artery bypass grafting (CABG) relieved angina. In summary, coronary arteritis occurs in SLE and may be part of a generalized arteritic picture or limited to the heart alone. Serial angiography delineates its rapidly changing course and even total occlusion may resolve following steroid treatment. Premature accelerated coronary atherosclerosis also occurs and is closely related to steroid treatment and acquired hypertension. In some of these pts, CABG may relieve symptoms.

DIVERGENT LEFT VENTRICULAR RESPONSE TO EXERCISE IN CHILDREN WITH LEFT VENTRICULAR PRESSURE OR VOLUME OVERLOAD
J.A. Breitweser, M.D., R.C.Boerth, M.D., T.P.Graham,Jr., M.D.,FACC, J.T. Weinberger, D.J. Petty, Division of Pediatric Cardiology, Vanderbilt Medical Center, Nashville TN 37232

Although exercise (EX) induced left ventricular (LV) dysfunction has been observed in adults with aortic regurgitation (AR), in children, this and the LV response to EX in patients with aortic stenosis (AS) have not been clearly characterized. To better determine these responses, we performed supine bicycle EX on 6 patients (pt) with AS (11.3±1.4 years): 3 moderate valvar, 2 moderate supravalvar, and 1 mild subvalvar, and 5 pt with AR (11.3±2.2 years): 5 moderate and 1 severe with mild mitral insufficiency. Their heart rates (HR), total work capactities (TWC), and echographic LV end-diastolic dimension (LVED) and shortening fractions (SF) were compared to results in 11 normal children (nl)(11±1 years). Pt with AS had TWC and HR increase of 3380±610 KPM/M^2 and 80±7 BPM ($\bar{x}$ ±SEM) respectively which were virtually the same as nl (3843± 749 KPM/M^2 and 88±10 BPM). The TWC and ΔHR of pt with AR were insignificantly lower than nl (2560±870 KPM/M^2, 58± 10 BPM), but EX was stopped in 1 pt because of a systolic BP > 230 mm Hg. Resting LVED of pt with AR(58±6.2 mm)was significantly($p < 0.01$)larger than that of nl (42±2.1 mm) or AS(39±1.4mm). All LVED decreased with EX. At rest, SF of pt with AS(42±2%) was not significantly larger than that of nl (39±2%), nor was the SF of pt with AR(34±3%) significantly less than nl. However, at maximal EX, pt with AS had SF of 53±3% which was significantly greater ($p < 0.05$) than that of nl (46±1%). In contrast, pt with AR had SF of 33±3% which was significantly lower than nl ($p < 0.01$). These findings confirm the EX induced LV dysfunction in children with AR, and suggest a hypercontractile LV response to EX in children with AS.

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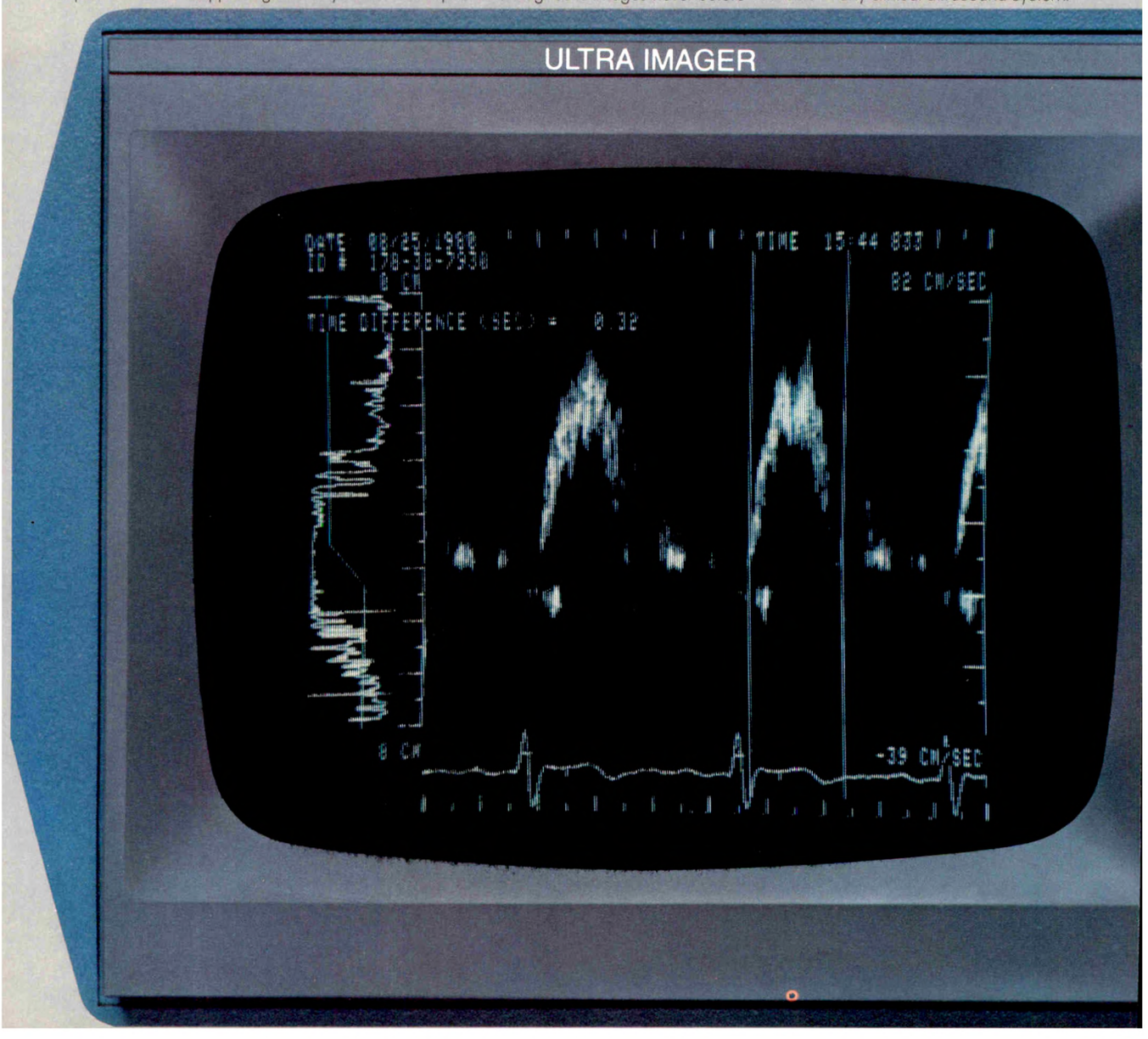


MORPHOLOGICAL-CLINICAL CORRELATES OF MYOCARDIAL FIBROSIS DUE TO DISCRETE SUBAORTIC STENOSIS IN NEWFOUNDLAND DOGS

Michael Jones, M.D.; Victor J. Ferrans, M.D.; William C. Roberts, M.D., FACC; A. Michael Borkon, M.D.; Joseph E. Pierce, D.V.M., National Heart Institute, Bethesda, Md.

We investigated the clinical and morphological interrelationships of myocardial fibrosis in infracoronary LV obstruction (LVOTO) due to discrete fibrous subaortic stenosis in Newfoundland dogs. Group I (n = 16) had no LVOTO, aged 4 to 61 months (mean 28 months), had LV/body weights of 3.3 ± 0.6 g/kg, had minimal interstitial fibrosis, and normal intramural coronary arteries. Group II (n = 12) had LVOT gradients of 50 - 95 mm Hg, aged 12 - 78 months (mean 27 months), and had LV/body weights of 6.4 ± 0.5 g/kg. In these dogs with LVOTO the LV mural and septal myocardium had replacement fibrosis, prominent perivascular fibrosis, and intramural coronary arteries with fibromuscular intimal hyperplasia. Group III (n = 16) suffered sudden death, aged 4 - 65 months (mean 27 months), had morphologic evidence of LVOTO, and LV/body weights of 5.7 ± 0.7 g/kg. Besides prominent interstitial fibrosis, these dogs had marked replacement fibrosis, recent myocardial necrosis, and intramural coronary arteries with fibromuscular hyperplasia in the septum and LV free wall. Extramural coronary arteries in all dogs were normal. Total LV blood flow, determined by radioactive microspheres, was not significantly different in 6 dogs with and 6 dogs without LVOTO (0.70 ± 0.09 versus 0.76 ± 0.14 ml/g/min); however, endocardial/epicardial flows for dogs with no LVOTO were 1.10 ± 0.09 versus 0.86 ± 0.04 for dogs with LVOTO ($p < 0.05$). Thus, our observations in this animal model of human infracoronary aortic stenosis indicate that LVOTO progresses to LV hypertrophy, intramural coronary arterial obstruction, myocardial fibrosis, and sudden death.

MORPHOMETRIC ANALYSIS OF LUNG BIOPSY TISSUE IN CANDIDATES FOR FONTAN-TYPE SURGICAL PROCEDURES

Marlene Rabinovitch, M.D.; Stephen P. Sanders, M.D.; Aldo R. Castaneda, M.D., FACC; and Lynne Reid, M.D., Children's Hospital Medical Center, Boston, MA

Lung biopsy tissue was obtained at cardiac surgery from 21 patients with either tricuspid atresia (TA) or single ventricle (SV) and analyzed, using morphometric techniques, to determine (a) whether pulmonary vascular changes were present which might result postoperatively in elevated resistance (Rp) and (b) the conditions under which these changes were likely to occur. In 10/13 TA patients, only abnormal extension of muscle into peripheral arteries (Grade A), was observed; 9/10 have undergone Fontan-type surgical procedures (FP), all with excellent hemodynamic results, in spite of preoperative mean pulmonary artery pressure ($\bar{P}_{Pa}$) values as high as 28 mmHg. The remaining 3/13 patients had impaired growth of the peripheral arteries (Grade C) and Heath Edwards ≥Grade III changes in at least one lung. All had had large Waterston shunts of >5 years' duration. Only 1/3 patients had an FP and he died in congestive heart failure. Three of 8 SV patients had only Grade A changes; all underwent FP but 2/3 died largely due to technical difficulties at surgery. The remaining 5/8 patients had, (in spite of preoperative $\bar{P}_{Pa}$ values as low as 10 mmHg), Grade C changes with eccentric intimal hyperplasia and recanalized thrombi in the intra-acinar arteries of at least one lung. All had had tight PA bands or inadequate shunts; 2 had severe polycythemia (hematocrit >70%). Both patients with FP died; no technical difficulties were identified. We conclude that severe pulmonary vascular changes may occur in TA or SV patients with either excessive or inadequate pulmonary blood flow; they may not be predicted from preoperative hemodynamics but may result in postoperative elevation in Rp, precluding a favorable result from a Fontan-type procedure.

RECIPROCAL DEVELOPMENT OF 4TH AND 6TH AORTIC ARCHES IN PULMONARY ATRESIA WITH VENTRICULAR SEPTAL DEFECT

Gaetano Thiene M.D., Carla Frescura M.D., Uberto Bortolotti M.D., Alessandro Del Maschio M.D., Marialuisa Valente M.D., University of Padova, Italy

25 specimens of pulmonary atresia with ventricular septal defect (PAVSD) have been studied by gross examination, microangiography and histology in order to establish whether a relationship exists between the extreme obstruction of the right ventricular outflow, the development of the aortic arch (AA) system and pulmonary arterial supply. The results of our study indicate that: 1) when ductus arteriosus (DA) is absent the lungs are entirely supplied by systemic collateral arteries (SCA); 2) DA and SCA do not coexist in supplying the same lung; 3) the peripheral pulmonary vessels function for gas exchange regardless the source of blood supply. In the normal development of the arterial pole of the heart, only the 4th and 6th AAs persist to join 2 separated ventricular bloodstreams to the descending aorta; the pulmonary arterial plexus develops in situ connecting first with the descending aorta through SCA and then to the pulmonary trunk through the 6th AA. In PAVSD both ventricular outputs are forced into the 4th arch; this is likely to explain the partial or complete involution of the 6th arch accounting for the cases with absent DA and for those with absent DA and pulmonary arteries. Accordingly the pulmonary arterial circulation maintains its primitive source of blood supply through SCA.

MORPHOLOGIC FEATURES OF THE DUCTUS ARTERIOSUS AFTER PGE_1 ADMINISTRATION FOR DUCTUS DEPENDENT CONGENITAL HEART DISEASES

InSook Park, MD, Michael R. Nihill, MD, FACC, Jack L. Titus, MD, The Lillie Frank Abercrombie Section of Pediatric Cardiology, Department of Pediatrics and the Department of Pathology, Baylor College of Medicine, and Texas Children's Hospital, Houston, Texas.

Histologic evidence of damage to the ductus arteriosus (DA) has been reported in neonates with ductus dependent congenital heart defects (CHD) after the use of Prostaglandin E_1 (PGE_1); the reported changes suggested structural weakening of the DA that might render it prone to laceration or rupture. We studied the morphology and histology of the DA in two groups of neonates with ductus dependent CHD. Group I was 12 neonates who received PGE_1 and died within 4 days after PGE_1 were discontinued. Mean duration of PGE_1 administration was 17 hrs (range from 30 minutes to 40 hours). Group II was 8 neonates who did not receive PGE_1 and were matched with group I for age, weight, type of CHD, and age at death. The gross morphology and histology of the DA were examined without knowledge of the clinical history. The length and internal diameter of DA were greater in PGE_1 group than control group ($P<0.15$). Histological staging of maturation (stage 1 being most immature; stage 4 being most mature or closing) showed that group I DA were significantly less mature than group II (mean stage 1.64 ± 0.32 vs 2.94 ± 0.33 $P<0.005$). Pathological findings reported in the previous study were not found in either group. We conclude that PGE_1 administration may delay the normal closing process or maturation of the DA but does not have any significant deleterious effect morphologically. Clinical follow up of 54 survivors up to 33 months after PGE_1 treatment suggest that the ductus closes normally after PGE_1 is discontinued with no deleterious sequele.

WEDNESDAY, MARCH 18, 1981
AM
VENTRICULAR ARRHYTHMIAS I: ASSESSMENT OF SUSCEPTIBILITY
8:30-10:00

ANATOMIC AND ELECTROPHYSIOLOGIC CORRELATES OF VENTRICULAR TACHYCARDIA REQUIRING LEFT VENTRICULAR STIMULATION
Michael E. Cain, MD; James F. Robertson, MD; Leonard N. Horowitz, MD, FACC; John A. Kastor, MD, FACC; Mark E. Josephson, MD, FACC, Hospital of the University of Pennsylvania, Philadelphia, Pa.

Therapy of ventricular tachycardia (VT) based on results of programmed ventricular stimulation (PVS) requires reproducible initiation of VT. With a ventricular stimulation protocol of single and double extrastimuli at 3 cycle lengths and bursts of rapid pacing to cycle lengths of 250 msec, 12 of 108 patients (11%) with reproducible initiation of VT required LV-PVS for initiation. The clinical, ECG, anatomic and electrophysiologic features of the 96 patients induced by RV-PVS (Group A) were compared to the 12 patients (Group B) in whom VT was only induced by LV-PVS. There were no significant differences between Groups A and B in incidence of coronary artery disease (81% vs 100%), anterior (59% vs 73%) or inferior (54% vs 45%) myocardial infarction, presence of aneurysm (67% vs 50%) or mean LV end diastolic pressure (17±9 vs 12±6 mm/Hg). Comparison of electrophysiologic parameters revealed no significant differences in mean A-H intervals (92±22 vs 89±15 msec), H-V intervals (59±15 vs 59±15 msec), RV effective refractory periods (RV-ERP 241±38 vs 260±40 msec) and LV-ERP (232±28 vs 251±43 msec) between Groups A and B respectively. VT with right bundle branch block and superior axis was more frequent in Group B (91% vs 32%, $p<.001$) but was also observed in 32 patients in Group A. We conclude that 11% of patients will require LV-PVS to initiate VT. No clinical, anatomic, ECG or electrophysiologic features predict whether LV-PVS will be required. Since VT initiation by PVS has important prognostic and therapeutic implications, LV-PVS should be performed when VT is not initiated by RV-PVS.

SIGNIFICANCE OF REPETITIVE VENTRICULAR RESPONSES INDUCED BY ATRIAL AND VENTRICULAR PACING IN PATIENTS WITH AND WITHOUT VENTRICULAR TACHYCARDIA.
Gerald V. Naccarelli, MD; Eric N. Prystowsky, MD, FACC; Warren M. Jackman, MD; Robert L. Rinkenberger, MD; James J. Heger, MD; Douglas P. Zipes, MD, FACC, Krannert Institute of Cardiology, Indiana University School of Medicine, Indianapolis, Indiana.

The purpose of this study was to determine: 1) the prevalence of repetitive ventricular responses due to non-bundle branch reentry (nBBR) and bundle branch reentry (BBR) induced by a single ventricular stimulus during atrial (AP) and/or ventricular pacing (VP) in pts with and without ventricular tachycardia (VT); and 2) the prognostic significance of nBBR in VT and non-VT pts. The prevalence during a drug free control state was:

	VT Patients(N=47)		NON-VT Patients(N=50)	
	VP(N=47)	AP(N=27)	VP(N=50)	AP(N=21)
nBBR	33(70.2%)	9(33.3%)	15(30.0%)	1(4.8%)
BBR	22(46.8%)	1(3.7%)	28(56.0%)	2(9.5%)

To determine if nBBR predicted future symptomatic VT or sudden death (SD), 59 VT pts had a discharge study and were followed for a mean of 10.3 months.

VP(N=59)	AP(N=33)
35 nBBR+ → 11 VT, 6 SD	11 nBBR+ → 6 VT, 2 SD
24 nBBR- → 5 VT, 1 SD	22 nBBR- → 7 VT, 2 SD

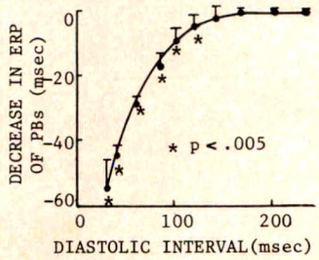
In the non-VT group no pt had a symptomatic event although 30.0% had nBBR induced during VP. In 16 VT pts who had VT induced on discharge study, 8 pts had nBBR on AP and 8 did not. Spontaneous VT/SD occurred in 7/8 (87%) who had nBBR on AP, but only in 2/8 (25%) who did not ($p<.05$). Conclusions: 1) in pts with VT, the induction of nBBR during VP is more sensitive, during AP more specific; however, neither technique alone is adequately predictive; 2) induced VT associated with nBBR on AP may define a high risk group.

REFRACTORINESS OF PREMATURE AND NONPREMATURE BEATS IN THE HUMAN VENTRICLE.
James R. Foster, MD, FACC, Ross J. Simpson, Jr., MD, and Leonard S. Gettes, MD, FACC, University of North Carolina, Chapel Hill, NC

Despite the critical role of premature beats(PBs) in initiating ventricular arrhythmias, much less is known about electrophysiology of PBs than about nonpremature beats(NPBs). On the basis of previous single fiber studies we hypothesized that refractoriness(R) of PBs having long coupling intervals(CIs) differs little from R of NPBs, but that R of early PBs shortens progressively as CI decreases.

We tested this hypothesis in two ways. First, we defined strength-interval(SI) curves of NPBs and of PBs having several CIs during electrophysiologic study in 12 patients (pts). As compared to SI curves of NPBs and late PBs, SI curves of early PBs were shifted significantly ($p < .005$) leftward toward shorter CIs.

Second, we measured the effective refractory period (ERP, shortest CI producing a response at 10mA) of PBs at multiple (6-10) diastolic intervals(DIs) in 6 pts. [The DI is a way of normalizing the coupling interval to the ERP of the NPB(ERP-NPB) and equals CI minus ERP-NPB] The figure plots the relationship between DI and the mean ±SD decrease (from ERP-NPB) in the ERP of PBs. The figure shows that R of PBs decreases little at long DIs, but decreases rapidly as DI approaches ERP-NPB.



Conclusions: 1) refractoriness of early PBs is much shorter than that of late PBs; 2) since early PBs may conduct very slowly, this marked shortening of their refractoriness may be an important determinant in the genesis of re-entrant ventricular tachyarrhythmias.

FRAGMENTED ELECTRICAL ACTIVITY-RELATIONSHIP TO VENTRICULAR TACHYCARDIA
Scott R. Spielman, MD; William J. Untereker, MD,FACC; Leonard N. Horowitz, MD,FACC; Allan M. Greenspan, MD,FACC; Michael B. Simson, MD,FACC; John A. Kastor, MD,FACC; Mark E. Josephson, MD,FACC. Hospital of the University of Pennsylvania, Philadelphia, Pa.

Endocardial activation mapping was performed in normal sinus rhythm at 12 left ventricular (LV) sites in each of 17 patients (pts) - Group I: 5 pts without myocardial infarction (MI); Group II: 5 pts with prior MI but without arrhythmias; and Group III: 7 pts with MI and recurrent sustained ventricular tachycardia (RSVT). In Group I pts discrete electrograms were recorded at all sites while in 3/5 Group II pts and 7/7 Group III pts fragmented electrograms (high frequency, low amplitude {1mV}, prolonged {>50 msec} potentials with no discrete intrinsicoid deflections) were consistently recorded within infarcted zones. Zero-5 (m=2.4±2.4) electrograms were fragmented in Group II pts compared to 4-9 (m=5.6±2.2) electrograms in Group III pts ($p<.05$). The duration of the most fragmented electrograms ranged from 75-90 msec (m=78±2.7) for Group II pts and 95-170 msec (m=131.4±28.7) for Group III pts ($p<.01$). The total duration of LV endocardial activation was 32-53 msec (m=41.6±9.6) for Group I pts, 23-95 msec (m=67±33) for Group II pts, and 95-200 msec (m=150±38.4) for Group III pts. We conclude that fragmented electrical activity: 1) is common in infarcted zones, 2) is longer in duration and more extensive in pts with RSVT and 3) may be due to slow conduction, a substrate for reentrant arrhythmias.

REPRODUCIBILITY OF ELECTROPHYSIOLOGIC RESPONSES TO PROGRAMMED VENTRICULAR STIMULATION DURING SERIAL DRUG TESTING IN PATIENTS WITH RECURRENT VENTRICULAR TACHYCARDIA

Jeremy N. Ruskin, MD, FACC, John P. DiMarco, MD, Hasan Garan, MD, Cardiac Unit, Massachusetts General Hospital, Boston, Mass.

The reproducibility of electrophysiologic responses to programmed ventricular stimulation (PVS) was examined in 22 consecutive patients with recurrent ventricular tachycardia (VT) in whom PVS-inducible VT was fully suppressed by at least one antiarrhythmic drug (AAD) regimen. PVS consisted of 1 and 2 premature right ventricular stimuli delivered during sinus rhythm, atrial pacing, and right ventricular apical pacing, as well as brief (3-5 beat) bursts of rapid ventricular pacing at 150-280 beats per minute. VT was initiated reproducibly by PVS off AAD in all patients and was sustained in 14 patients and nonsustained in 8 patients. During serial AAD testing, VT was initiated by PVS an average of 4 times (range 1-10), each on separate days, in all 22 patients. In all 22 patients, complete suppression of PVS-inducible VT was achieved with an AAD regimen. Repeat PVS on the same AAD regimen was carried out 1 to 4 days later in all patients. Patients were retested randomly with regard to the time of their last AAD dose. In 21 of 22 patients (95%), repeat PVS revealed persistent noninducibility of VT; whereas, in 1 patient VT was inducible during repeat testing on the same AAD regimen. These observations demonstrate that the complete suppression of PVS-inducible VT by an AAD regimen is a highly reproducible finding when PVS is repeated at 1 to 4 days.

WEDNESDAY, MARCH 18, 1981
AM
CORONARY ARTERY SPASM
8:30-10:00

HOW USEFUL IS THE ELECTROCARDIOGRAM AS AN INDICATOR OF CORONARY ARTERY SPASM?

Robert L. Feldman, MD; James Hill, MD; Carl J. Pepine, MD, FACC; C. Richard Conti, MD, FACC, Univ. of Florida and VA Medical Center, Gainesville, FL.

Transient changes of the electrocardiogram (ECG), usually manifest as significant ST shifts ($\geq$ 1mm), occurring during rest angina are sought as evidence for myocardial ischemia. Frequently, in patients with rest angina, the basis for transient myocardial ischemia has been shown to be coronary artery (CA) spasm (S). During catheterization performed to further evaluate the basis for angina, we found 7 patients who had rest angina accompanied by CAS (transient 100% obstruction of a major coronary artery in 4 patients or diffuse >50% diameter narrowing in 3 patients). During the episode of rest angina associated with CAS, none (0 of 7) of these patients had significant ST shifts in standard limb (I-AVF) and selected precordial ECG leads compared to ECGs recorded during pain-free intervals occurring immediately before or after relief of angina and reversal of CAS. At other times, each patient also had at least five 12 lead ECGs recorded during rest angina and at least two 24 hour dual-lead ambulatory monitor ECG recordings on days when they had angina. Again, no significant ST shifts were found during rest angina in 3 patients. In the other four patients ST shifts were found during <20% of the rest pain episodes observed.

These findings suggest that the ECG has important limitations as an indicator of myocardial ischemia associated with CAS in selected patients with rest angina. The absence of significant ST shifts during rest pain does not necessarily exclude CAS.

CONTRASTING EFFECTS OF PROCAINAMIDE AND VERAPAMIL ON INTRAVENTRICULAR CONDUCTION AND REENTRY

C. Pratap Reddy, MD, FACC; Borys Surawicz, MD; Russell G. McAllister, MD, FACC, Veterans Administration and University of Kentucky Medical Centers, Lexington, KY

The effect of intravenous Procainamide (PA) (8-14 mg/kg) and Verapamil (V) (0.075-0.15 mg/kg) on intraventricular conduction and reentry (Re) within the His-Purkinje System (HPS) were studied in 23 patients (pts) utilizing His (H) bundle electrograms and ventricular extrastimulus method. PA was studied in 13 pts and V in 10 pts. Data (in msec) for both groups are shown below.

	PA	V
Zone of Re	68±18 vs 33± 8*	60±20 vs 56±22+
Critical V_2H_2	214±27 vs 286±13*	194±15 vs 196±14+
Longest V_2H_2	253±26 vs 299±38*	254±19 vs 253±19+
QRS duration of V	128± 5 vs 136± 6*	129± 3 vs 139± 3+
Latency	15± 5 vs 21± 6*	18± 4 vs 130± 3+
	*<0.005	+>0.1

V produced significant prolongation of atrioventricular nodal (AVN) conduction (A-H interval: 91±12 vs 98±16; $p<0.05$) and refractoriness (functional refractory period of AVN: 396±44 vs 448±53; $p<0.001$) in all pts. CONCLUSIONS: 1) Whereas PA [plasma concentration (PC) 12±5 mg/L] significantly prolonged the duration of latency and intramyocardial (IM) and HPS conduction and narrowed the zone of Re, V in therapeutic PC (138±27 ng/ml) which caused significant prolongation of AVN conduction and refractoriness did not change the duration of latency and IM and HPS conduction and the zone of Re. 2) Slow channel dependent conduction plays no detectable role in propagation of even the earliest premature impulses delivered before the completion of repolarization of HPS and/or ventricular muscle.

EXPERIMENTAL CORONARY ARTERY SPASM IN INTACT DOG: ANGIOGRAPHIC CHARACTERIZATION, RECORDING OF FLOW, AND RESPONSE TO DIHYDROPYRIDINES

Julio E. Pérez, MD; Cynthia Lucas, BS; Philip D. Henry, MD, FACC, Washington University, St. Louis, MO.

An animal model for the study of coronary spasm was developed. Attempts to induce non-thrombotic, segmental spasms by infusing constrictors into major coronary arteries (8 dogs) or by electrically stimulating the vessels with ring electrodes (4-16 Hz; 9 dogs) were unsucessful. Therefore, effects of direct application of drug to the surface of the vessels were evaluated. Three cm long segments of the left anterior descending coronary artery of open-chest dogs (n=9) were covered with ion exchange gels containing adsorbed ions or drugs. Coronary flow was monitored with a proximal electromagnetic flow probe. SP-Sephadex in the K^+-cycle decreased flow by 38 ± 7% (SE; $p < .01$), whereas the same gel in the Na^+-cycle had no effect. K^+-induced spasms were relieved by removal of the gel, and the spasms were reproducible on repeated applications. Ventricular pressure, dP/dt, and heart rate remained unchanged. Peak reactive hyperemia after complete occlusion for 15 sec was decreased by 68 ± 7% compared to the response before spasm ($p < .001$). Selective coronary arteriography during spasm revealed the internal diameter of the treated segment to be reduced by 21 ± 6% ($p < .01$). Equihypotensive doses of nitroglycerin (50 µg/min, i.v.), nifedipine (1 µg/min, i.v.), and BAY k 5552 (.2 µg/min, i.v.) increased flow during spasm by 33 ± 4%, 95 ± 8%, and 186 ± 18%, respectively. Nitroglycerin produced partial, and the dihydropyridines complete relief of the spasms on angiography. Thus, reversible segmental spasms were documented by arteriography, and the new dihydropyridine derivative BAY k 5552 was shown to be a very potent spasmolytic agent.

ORONARY VASOSPASM PROVOKED BY THE HYPERVENTILATION TEST. uillermo Pujadas, MD, FACC; Alberto Tamashiro, MD; José uades, MD; José Aldasoro, MD. Laboratorio de Hemodinámica ospital Italiano de Buenos Aires, Argentina.

he purpose of this paper was to investigate with which requency alkalosis provoked by hyperventilation performed uring 5 minutes (HV) induces coronary artery spasm (CAS) n patients with angina pain. Method: The patient hyperentilates while the ECG is continuously monitored (L_2-V_5) until: 1)ST segment elevation≥1mm. or seudo-normalzation of an inverted T wave occurs; 2)ST segment depresion≥2mm. appears; 3)the 5 minutes of HV as well as 15 miutes of follow-up elapsed and no repolarization changes ppeared or if there were changes they did not follow the wo previous patterns. A coronary angiogram was performed efore, inmediately after the HV and 5 minutes after ,6 mg. of nitroglycerine administered sublingually. The ngiographic findings were reported as: 1)Localized spasm LS); 2)Diffuse narrowing (DN) -mild when it reduced the rteries diameter between 20 and 50%; severe>50%-. esults: The HV test was performed in 59 patients, CAS ocured in 17 (29%): 13 patients with LS, 2 with severe DN, nd 2 with mild DN. Results according to the clinical ubset: In atypical angina 15% (4/27) had CAS (1 LS, 1 sere DN, and 2 mild DN). In Prinzmetal's angina (angiographically normal arteries) the 2 patients had LS. Only of the 10 patients with stable angina had CAS (mild LS), ut in unstable angina 67% (6/9) had CAS (5 LS and 1 sere DN). In the subset of slowly progressive angina -angina that worsens slowly in weeks or months- 36% (4/11) of atients had CAS, all LS. The CAS was easily relieved by itroglycerine in all patients. Conclusions: Coronary ngiography demostrates that the hyperventilation test rovokes vasospasm with similar frequency than the one reorted in the literature for the ergonovine test. Coronary pasm appears more frequently in unstable angina.

EFFECTS OF COLD-PRESSOR TEST ON REGIONAL CORONARY HEMODYNAMIC AND ANGIOGRAPHIC RESPONSES. Robert L. Feldman, MD, James L. Whittle, M.D., Carl J. Pepine, MD, FACC, C. Richard Conti, MD, FACC, Univ. of Florida and VA Medical Center, Gainesville, Florida.

To more clearly define the effects of the cold pressor test (CPT) on the coronary circulation, coronary sinus (CSF) and great cardiac vein (GCVF) flows (F), aortic (Ao) and left ventricular (LV) pressures (P) and epicardial and small (0.3±1.0 mm) intramyocardial coronary artery (CA) diameters were measured in 12 patients. Determinations were made before and after CPT. CSF and GCVF were used as indices of total and anterior LVF and CSF-GCVF as an index of inferior F. Perfusion of LV regions was considered potentially "normal" (nl) or "abnormal" (abn) based on the presence or absence of ≥50% narrowing in the CA supplying a given region. Perfusion was potentially "nl" in 14 and "abn" in 10 regions. With CPT, heart rate (5 beats/min), mean AoP (23 mmHg) and LV-end-diastolic P LVEDP (6 mmHg) increased, all $p<0.05$. "Nl" region LVF increased (72±46 to 94±50 ml/min, mean ±SD) as resistance (CR) decreased (2.63±2.78 to 2.31±2.43 mmHg/ml/min), both $p<0.05$. "Abn" region LVF was unchanged (55±22 to 53±15 ml/min, p=NS) and CR increased (2.15±0.84 to 2.63±0.77 mmHg/ml/min, $p<0.05$). CA diameter decreased only minimally in both "nl" (6±9%) and "abn" (8 11%) regions, both $p<0.05$. Furthermore, both "nl" and "abn" region angiographic responses were similar (p=NS). These data show that CPT increases CR in angiographically defined potentially "abn" regions. These increases in CR are not due to CA "spasm" but may be due to a differential effect of an increased LVEDP on regional blood flow.

LINICAL USE OF ALCALOSIS AS A PROVOCATIVE TEST OF CORONARY SPASM.
imon Weber MD, Alain Guiomard MD, Bernard Lancelin MD, lorent de Vernejoul MD, René Gourgon MD, Michel egeorges MD. University René Descartes School of Medecie, Paris, France.

Alcalosis (ALC) was used as a provocative test of coronary spasm in 70 patients (pts) (mean age 56) with angina t rest. Rapid infusion of 200 ml. Tris Buffer immediately followed by 5 minutes of maximal hyperventilation raied arterial pH to 7.67 ± 0.05. ALC induced chest pain nd ischemic ECG changes in 24 pts : ST elevation in 10 ts and ST depression in 14. Ischemic changes occurred du ing hyperventilation in 16 pts and within 3 minutes afer its discontinuation in 8. During hyperventilation eart rate increased from 66 ± 11 to 71 ± 14 ($p<0.01$) ut systolic arterial pressure decreased from 139 ± 12 mHg to 130 ± 12 mmHg ($p<0.01$) and thus the rate-pressue product did not change. (9130 ± 1750 versus 990 ± 2690. NS.). In all cases pain and ECG changes reressed within a minute, after 1 mg intravenous nitroglyerin. Coronary arteriography documented significant ≥70 %) stenosis in 21 pts ; 3 pts had normal angiograms ut 0.4 mg of methylergometrine induced coronary and ECG hanges similar to ALC.

ALC was repeated in 16 of the 24 positive responders ne hour after oral administration of 20 mg of the calium antagonist Nifedipine and was then constantly negative. We conclude that ALC can be used in a coronary care nit as a provocative test of coronary spasm. Response to LC may contribute to determine the mechanism of angina t rest, to choose the optimal medical therapy and to ass its efficiency.

CORONARY ARTERY SPASM: AN ISOLATED PHENOMENON OR ONE MANIFESTATION OF A MORE DIFFUSE VASCULAR HYPERREACTIVITY? Joaquin Arciniegas, MD; William C. Little, MD; H. Cecil Coghlan, MD; Richard O. Russell, Jr., MD, FACC; Charles E. Rackley, MD, FACC; John A. Mantle, MD, FACC. Division of Cardiology, University of Alabama in Birmingham, Birmingham, Alabama.

To investigate a possible association of coronary artery spasm with other vasospastic disorders, the frequency of vascular headaches and Raynaud's phenomenon was determined in 43 patients with chest pain who were evaluated for the presence of coronary artery spasm. Eighteen patients (Group I) had coronary artery spasm documented by ST abnormalities during spontaneous chest pain or with ergonovine stimulation tests. Twenty-five patients (Group II) had no evidence of coronary artery spasm despite ergonovine stimulation. Group I and II were similar in mean age (54 vs 48 yrs), sex ratio (10 males, 8 females vs 14 males, 11 females), and presence of greater than 50% luminal diameter coronary artery stenosis (38% (7/18) vs 36% (9/25)). Vascular headaches or Raynaud's phenomenon was present in 39% (7/18) in Group I and 8% (2/25) in Group II ($p<.025$). Vascular headaches occurred in 16% (3/18) of Group I and 4% (1/25) of Group II (p=NS). Raynaud's phenomenon was present in 38% (5/13) of Group I and 4% (1/25) of Group II ($p<.05$). All four of the patients with Raynaud's phenomenon who received nifedipine for coronary artery spasm noted relief of Raynaud's phenomenon concomitant with relief of chest pain. The strong association between coronary artery spasm and other disorders with increased vascular reactivity suggests a common etiology.

In summary: 1) Disorders characterized by increased vascular reactivity frequently coexist with coronary artery spasm; 2) Nifedipine was useful in controlling Raynaud's phenomenon as well as chest pain in these patients.

WEDNESDAY, MARCH 18, 1981
AM
ADULT CARDIOLOGY/CLINICAL STUDIES
8:30-10:00

COMPUTED TOMOGRAPHY. A USEFUL TECHNIQUE FOR FOLLOW-UP OF BOTH MEDICALLY AND SURGICALLY TREATED PATIENTS WITH THORACIC AORTIC DISSECTION. Martin Lipton, MD; Kevin Turley, MD, FACC; J. David Godwin, MD; Erik Carlsson, MD; Paul A. Ebert, MD, FACC; John C. Hutchinson, MD, FACC, University of California, San Francisco, CA 94143.

Dissection of the thoracic aorta represents the most common catastrophic event involving the great arteries. Improvements in both surgical management and the use of antihypertensive therapy have improved early survival. However, persistence of the false lumen has been demonstrated in a high percentage of the surgically treated patients (85%) and the reentry point remains in those medically managed. Thus, the persistent risk in both medically and surgically treated patients of expansion and redissection must be monitored. Computed tomography uses the technique of CAT scanning at multiple levels of the thoracic and abdominal aorta coupled with contrast injection to demonstrate both true and false lumen perfusion at each level, and then special computer programs to reconstruct the thoracic and abdominal aorta in the longitudinal plane. Grafts, intimal flaps, and false lumen perfusion are clearly delineated. 16 patients, 11 with surgically treated thoracic-aortic dissections, and 5 patients with medically treated dissections (i.e. antihypertensive therapy) have been evaluated using this modality. The studies demonstrate persistence of the false lumen in 11 patients, with definition of aortic intimal and adventitial size in both these patients and in those with clotted false lumens. This technique affords a reproducible profile of the anatomy of the involved areas, both in the transverse plane of the CAT scan at specific levels, and reconstruction in the longitudinal plane of the thoracic and abdominal aorta, thus avoiding the need for repeated arteriograms for follow-up of aortic size and false lumen.

REVERSIBLE SEGMENTAL CONTRACTION ABNORMALITIES DURING EXERCISE INDUCED CORONARY ARTERY SPASM AND THEIR EFFECT ON GLOBAL LEFT VENTRICULAR FUNCTION.
Robert A. Chahine, MD, FACC; Mario S. Verani, MD, FACC; Nadim M. Zacca, MD, FACC; Albert E. Raizner, MD, FACC; Felix Pircher, MD; Richard R. Miller, MD, FACC; Robert J. Luchi, MD, FACC, Baylor College of Medicine and VAMC, Houston, Texas.

Very few observations have been published concerning the effect of coronary artery spasm (CAS) on left ventricular (LV) contraction. Accordingly, 4 patients (pts) with angiographically documented recurrent exercise (EX) induced CAS resulting in transient total or near total occlusion of a major vessel underwent gated radionuclide ventriculograms (RNVG) at rest (RT) and during EX-induced CAS. In two pts the CAS involved a proximal segment of the left anterior descending coronary artery (LAD) and in the other 2 pts, it involved the mid right coronary (RCA).

Detailed analysis of the RNVGs revealed marked wall motion abnormalities during EX-induced CAS, involving predominantly the septum and the antero-lateral wall in the 2 pts with LAD spasm while in the 2 pts with RCA spasm the contraction abnormalities involved primarily diaphragmatic segments. In the pts with LAD spasm LV ejection fraction (EF) decreased respectively from 51% and 70% at RT to 41% and 42% after EX. In the other 2 pts with RCA spasm EFs were 61% and 47% at RT and 62% and 50% respectively after EX. Repeat RNVG at RT, and with EX after nifedipine, demonstrated normalization of the CAS-induced contraction abnormalities.

Thus, CAS producing complete occlusion of a major coronary vessel results in segmental contraction abnormalities corresponding to the blood supply distribution. LAD spasm produces profound deleterious effect on global LV function as reflected by decreased EX-EF in contrast with RCA spasm which results in minimal effect.

HAEMODYNAMIC EFFECTS OF HAEMATOCRIT REDUCTION IN PATIENTS WITH CYANOTIC CONGENITAL HEART DISEASE AND SECONDARY POLYCYTHAEMIA.
Paul Oldershaw MRCP and Martin St. John Sutton MRCP. Brompton Hospital, London. SW3 6HP.

Patients with cyanotic congenital heart disease and secondary polycythaemia are subjectively improved by venesection. We have studied six such patients, both at rest and during exercise, to see if this subjective improvement is matched by haemodynamic changes. Haemoglobin concentration fell from 22.4±0.5g/dl (mean±SEM) to 18.8±0.5g/dl ($p<0.01$) 3 days after venesection with intravenous plasma replacement. Cardiac index, measured using the Fick Principle, increased from 2.2±0.1L/min/m^2 pre-venesection (Pr-V) to 2.9±0.2L/min/m^2 3 days post-venesection (Po-V), ($p<0.01$), without changes in resting heart rate. Exercise testing, using a cycle ergometer, showed an increase in maximal exercise capacity from 333±30Kpm/min Pr-V to 500±48Kpm PoV ($p<0.01$). During a constant work-load exercise test of six minutes duration, a greater mean cardiac index was produced post-venesection in response to the same work-load (6.7±.4L/min Pr-V, 7.3±.3L/min Po-V; $p<0.05$). Oxygen uptake during this test was also significantly increased (1053±69ml/min Pr-V, 1209±74ml/min Po-V; $p<0.05$) and oxygen debt reduced (863±68ml Pr-V, 622±78ml Po-V; $p<0.05$). Similar studies were performed at 14 days post-venesection; the above changes were maintained. These results show that the subjective improvement in cyanotic patients post-venesection is matched by objective circulatory changes, demonstrable both at rest and during exercise.

20 MONTH EXPERIENCE IN OUTPATIENT CARDIAC CATHETERIZATION. Earl S. Perrigo, M.D., Michael L. Kuehne, M.S., Francesco Michienzi, M.D., F.A.C.S. The Michienzi Medical Center, Sandusky, Ohio.

In a 20 month period, 224 cardiac catheterizations (209 brachial, 15 femoral) with coronary angiography were performed in this non-hospital outpatient laboratory. Catheterization revealed 119 (53%) patients with significant CAD, 31 (14%) with valvular heart disease, 9 (4%) with congenital heart disease, and 9 (4%) with cardiomyopathy. Following catheterization, 103 (46%) patients were placed on specific medical therapy and 55 (25%) were referred for cardiac surgical therapy. Quality of service was assured through the regular review of case reports and angiographic films by outside consultants and through submission of the data to a Cooperative Study of outpatient cardiac catheterization. There was a 2.6% complication rate with two diminished brachial pulses requiring surgical restoration and 4 catheterization induced arrhythmias requiring cardioversion. There were no catheterization related deaths. Cost of outpatient catheterization was found to be approximately 20% less than inpatient catheterization. Patients and families generally indicated a preference for this non-hospital setting. This study demonstrates that the non-hospital outpatient performance of cardiac catheterization does not compromise quality or safety of service, is cost effective, and has good patient acceptability.

INHIBITION OF LEUKOCYTE MIGRATION BY MONONUCLEAR CELL SUPERNATANTS FROM PATIENTS WITH ISCHEMIC HEART DISEASE. Sunil K. Das, M.D.; Leonard D. Stein, M.D.; Russell T. Reynolds, M.S.; Paulette J. Thebert, B.S.; James T. Cassidy, M.D., Departments of Medicine and Pediatrics, University of Michigan, Ann Arbor, MI.

Although Immunologic abnormalities have been observed in patients with various forms of ischemic heart disease (IHD), their clinical significance remain unknown. The present study examined in-vitro correlates of cell-mediated immunity (CMI) in 12 patients with unstable angina (UA); 5 with stable angina (SA); 12 with myocardial infarction (MI), 9 with MI < 1 year, 3 with MI > 1 year; and 12 control subjects (C). The indirect agarose leukocyte migration inhibition factor test was performed with the culture supernatants from peripheral blood mononuclear cells exposed to human heart extracts (HE) and concanavalin A (con A). Leukocyte migration inhibition (LMI) was present in response to HE for 6 of 12 (50%) patients with UA, 3 of 5 (60%) with SA, 5 of 12 (42%) with MI, and 1 of 12 (8%) of C. Migration indices ($\bar{X} \pm SD$) for these groups were measured at 0.9 ± 0.16 for UA, 0.88 ± 0.14 for SA, 0.9 ± 0.17 for MI, and 0.97 ± 0.1 for C ($P < 0.05$ between test groups and C). All patient groups had normal con A stimulated LMI. Thus LMI in response to HE stimulation provides additional evidence of altered immune response in patients with IHD probably related to previous or ongoing myocardial damage.

ACCELERATED CORONARY ATHEROSCLEROSIS FOLLOWING CARDIAC TRANSPLANTATION: SIGNIFICANCE OF HYPERCHOLESTEROLEMIA M.L. Hess, M.D., Andrea Hastillo, M.D., FACC, T.C. Wolfgang, MD, R.R. Lower, MD, Medical College of Virginia, Richmond, VA.

The significance of hypercholesterolemia in the development of accelerated atherosclerosis in patients following cardiac transplantation (CT) is unknown. To possibly identify those CT patients at increased risk for the development of accelerated coronary artery disease (CAD), total cholesterol (C), high density lipoprotein cholesterol (HDL) and the ratio of C/HDL were longitudinally followed in 15 long term survivors (>3 mos) of CT and correlated with graft function. Indications for CT: recurrent myocardial infarction (MI,n=7) and cardiomyopathy (CM,n=8). Preoperative C did not differ in the two groups (MI=201 ± 37; CM=151 ± 14 mg%, $p>0.2$) but HDL was lower in the MI group (29 ± 2.7 vs 46 ± 5.9 mg%, $p<0.05$) and R was greater (7.3 ± 1.3 vs 3.5 ± 0.3, $p < 0.05$). At one year post CT, both C and R were greater in the MI group (C: 350 ± 43 vs 221 ± 16 mg%, $p<0.05$; R: 6.8 ± 1.1 vs 3.8 ± 0.08, $p<0.05$). At two years post CT, C and R remained elevated in the MI group (C: 330 ± 29 vs 220 ± 11, $p<0.01$; R: 7.8 ± 0.8 vs 3.8 ± 0.8, $p<0.001$) and HDL was significantly decreased in the MI group (42.7 ± 2.0 vs 59.2 ± 6.0 mg%, $p<0.05$). All patients in the MI group and only one patient in the CM group developed either abnormal exercise thallium studies (segmental perfusion defects), gated pool scans (regional wall motion abnormalities) or myocardial infarction. It is concluded that the accelerated atherosclerosis of CT is associated with an increase in C and C/HDL ratio, that by two years post CT, patients with elevated C and R values demonstrate graft dysfunction with evidence of CAD and that patients transplanted for recurrent MI may be at increased risk for the development of accelerated CAD.

WEDNESDAY, MARCH 18, 1981
AM
ECHOCARDIOGRAPHY: VENTRICULAR FUNCTION I
8:30-10:00

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC MEASUREMENT OF EJECTION FRACTION: WHAT DETERMINES A GOOD CORRELATION? R. Brad Stamm, MD; Douglas L. Mayers, MD; Randolph P. Martin, MD, University of Virginia, Charlottesville, Va.

An estimate of left ventricular ejection fraction (EF) is often used. We performed two-dimensional echocardiography (2DE) on 45 patients 24 hours prior to ventriculography (LVG) to assess a) whether trained echocardiographers could accurately estimate EF, b) which measured 2DE formula correlated best with LVG, and, c) to determine if the quality of the 2DE study affected the EF. Three blinded readers estimated EF using all standard 2DE views. Additionally calculated area, diameter and length was measured from parasternal short axis and apical views. 2DE quality was graded good and poor. Correlation with LVG follows:

All patients N = 45	Patients Measured		Good Quality Studies Only		Poor Quality Studies Only	
	N	r	N	r	N	r
Estimated	45	.93	20	.94	25	.91
Simpsons	21	.93	16	.93	5	.84
Ellip Biplane 4	35	.85	16	.84	19	.91
Ellip Biplane 2	13	.91	11	.92	too few	
Ellip Uniplane 4	42	.87	20	.92	22	.80
Ellip Uniplane 2	17	.86	12	.90	5	.43
Short Ellipse	36	.87	20	.95	16	.74
Apical Diameters	17	.81	13	.89	too few	
Teicholz	36	.74	20	.76	16	.77
Length Estimate	34	.80	20	.83	14	.78

p=0.01 for all r

We conclude that a highly accurate 2DE estimate of EF can be made by trained observers; the estimated EF was obtained in all patients and was not affected by echo quality. The biplane echo formulas are the most accurate but they are adversely affected by echo quality and cannot be obtained in all patients.

HETEROGENEITY OF SEGMENTAL LEFT VENTRICULAR WALL THICKENING AND EXCURSION IN TWO-DIMENSIONAL ECHOCARDIOGRAMS OF NORMAL HUMANS. Natesa Pandian, MD; David Skorton, MD; Steve Collins, PhD; Ed Burke, PhD; Herman Falsetti, MD, FACC; Richard Kerber, MD, FACC, CV Cent, Univ of Iowa, Iowa City, Iowa.

Segmental abnormalities of left ventricular (LV) wall thickening and excursion have been demonstrated by 2-D echo (2DE) in ischemic heart disease, but the variability of segmental dynamics in normals has not been defined. We performed 2DE on 12 normal male subjects, age 19-27. Short-axis images at mitral valve (MV), chordal (CH) and papillary muscle (PM) levels were obtained at end-diastole and end-systole. Radii were drawn dividing each image into 12 equal segments. 420 segments were analyzed. % systolic wall thickening along each radius, and % area change of each cavity segment were determined, using a computerized analysis which corrected for cardiac rotation and translation. Variability was measured as the range of thickening or segmental area change % (highest-to-lowest) for each subject at each level. Average range for all subjects at each level is expressed as "mean range". Results: We saw greater than 15% cavity area change and greater than 20% systolic thickening in 95% of all segments analyzed.

	Wall Thickening (%)			Cavity Segment Area Change(%)		
Level	Mean	S.D.	Mean Range	Mean	S.D.	Mean Range
MV	53	27	76	44	16	32
CH	50	23	61	47	21	53
PM	53	23	64	52	20	43

Correction for cardiac rotation and translational motion within the thorax did not alter these results. Conclusions: 1) There is considerable intersegmental variability of LV dynamics in normals on 2DE. 2) Marked differences in thickening and wall excursion may occur in adjacent segments in normals, and therefore such differences alone do not indicate ischemic heart disease.

ACCURACY OF M-MODE ECHO MEASUREMENTS OF THE LEFT VENTRICLE. Mark J. Friedman, MD, FACC, William R. Roeske, MD, FACC, David J. Sahn, MD, FACC, Stanley J. Goldberg, MD, FACC. University of Arizona; Tucson, Arizona.
Although the minor diameter of the LV can be measured from an M-mode echo, criteria for measuring end diastolic diameter (EDD) & end systolic diameter (ESD) are controversial. Therefore, we simultaneously recorded an M-mode echo & sonomicrometer crystal signals & measured the LV in 12 instrumented open chested dogs. Crystals were placed on the endocardial surface of the septum & the LV posterior wall at the chordal level. An M-mode echo of the septum & posterior wall was obtained from the same level. M-mode echo EDD was measured at the onset of the QRS (EDD-Q), at the peak of the R-wave (EDD-R), & as the largest diameter (EDD-L). M-mode echo ESD was measured from the posterior motion of the septum (ESD-VS), from the anterior motion of the posterior wall (ESD-PW), and as the smallest diameter (ESD-S). Fractional shortening for all pairs of EDD & ESD was compared to crystal fractional shortening. EDD-Q (mean ± SD; 4.04±.6) and EDD-R (4.02±.6) were the same as crystal EDD (4.02±.7). However, EDD-L (4.34±.6) was larger than crystal EDD ($p < 0.01$). ESD-VS (3.25±.6) was the same as crystal ESD (3.28 ±.7). However, ESD-PW (3.21±.6) and ESD-S (3.0±.6) were smaller than crystal ESD ($p<0.05$ & $p<0.01$). Fractional shortening using EDD-Q or EDD-R with ESD-VS or ESD-PW was not different from crystal fractional shortening (.19 ± .05). All fractional shortening measurements using EDD-L or ESD-S were larger than crystal fractional shortening ($p<0.01$). CONCLUSION: M-mode echo EDD-Q or EDD-R and ESD-VS are best for estimating LV dimension & fractional shortening. These data support the recommendations of the American Society of Echocardiography in attempting to quantitate LV minor axis dimensions from the M-mode echo.

COLD PRESSOR ECHOCARDIOGRAPHY
Roberta G. Kurtz, M.D., Assoc., Mary Sue LeMire, RT., Robin Chene, Marie Stacewicz, Bertram Pitt, M.D., FACC, University of Michigan Medical Center, Ann Arbor, MI

M-Mode echocardiography has found wide application for the detection of resting left ventricular dysfunction (LVD). Although exercise (Ex) has also been found useful in evaluating patients with latent LVD, it has not found wide application because of technical difficulty. Recently Cold Pressor (CP) radionuclide ventriculography (RNV) has been proposed as an alternative to ExRNV and found to have a $> 90\%$ sensitivity and specificity for detecting latent LVD. A normal CPRNV is a $< .03$ absolute decrease in LV ejection fraction (EF) from a resting value of $\geq .50$ and no wall motion abnormality. The same criteria for a normal CP echo was used, calculating LVEF by the Teichholtz formula. Ten patients were evaluated by both CP Echo and CPRNV. Both CP Echo and CPRNV were normal in 3 and abnormal in 5 patients. Two patients had abnormal CP Echo but normal CPRNV, 1 with ergonovine proven coronary artery spasm of the left circumflex artery and the other with constrictive pericarditis, mitral valve prolapse, and normal coronary arteries. Thus, CP Echo may be a useful technique for detecting latent LVD without many of the technical difficulties encountered with Ex echocardiography.

SIMULTANEOUS CONTRAST TWO-DIMENSIONAL ECHOCARDIOGRAPHY AND CONTRAST VENTRICULOGRAPHY: DISCREPANCIES IN LEFT VENTRICULAR VOLUME
Michael J. Barrett, MD; Larry Jacobs; Jonathan Gomberg; Lynn Horton; Steven G. Meister, MD, FACC, The Medical College of Pennsylvania, Philadelphia, PA.

Previous non-simultaneous studies demonstrate the left ventricular volume (LVV) by two-dimensional echocardiography (2D Echo) differs significantly from that obtained by contrast ventriculography (CV). To investigate this problem, we performed simultaneous contrast 2D Echo and CV on 19 cardiac cycles in 8 patients. CV was recorded in the 30° right anterior oblique view simultaneous with contrast 2D Echo in the apical long axis view during a power injection of 45 cc of 76% Renografin. Independent observers traced the ventricular outlines in each technique and simultaneous beats were then matched. All perimeters of ventricular size were underestimated by 2D Echo compared to CV: Cavity length by 16.0% ± 2.9 (M ± SEM) ($p<.001$) endocardial area by 32.6% ± 3.5%, ($p<.001$) and ventricular volume by 40.5% ± 5.4, ($p<.001$). Linear regression analysis yielded a good correlation of stroke volume ($r=0.88$, SEE=15.6 cc) and ejection fraction ($r=0.90$, SEE=.08) between 2D Echo and CV. Since there was no fluctuation in LVV between studies and excellent endocardial definition by contrast 2D Echo, none of these errors can be attributed to these sources. However, previous studies in phantom hearts have shown 2D Echo increases apparent wall thickness with consequent reduction in cavity size. This reduction in cavity size may account for the observed differences in LVV between these two techniques. Conclusion: Simultaneous contrast imaging shows 2D Echo underestimates ventricular volume by 40% compared to contrast ventriculography. Regression equations permit an accurate calculation of stroke volume and ejection fraction by 2D Echo.

INFERIOR VENA CAVAL ULTRASONAGRAPHY: ITS USE IN THE ASSESMENT OF RIGHT HEART FUNCTION
Gary S. Mintz MD, FACC, Morris N. Kotler MD, FACC, Wayne R. Parry, Abdulmassih S. Iskandrian MD, FACC, Sally A. Kane RN, Cardiovascular Institute, Hahnemann Medical College, Philadelphia, Pennsylvania

We studied the inferior vena cava (IVC) as an index of right heart function. A two-dimensional echo sector visualized the IVC and its M-mode cursor generated a time-motion record of IVC size and pulsation. In 10 normal patients, small presystolic ("A") and systolic ("V") waves were recorded; the normal "A" wave was <125% and the normal "V" wave <140% end diastolic IVC dimension. Inspiration normally caused >50% decrease in IVC dimension. Seventy patients with mitral valve disease, coronary artery disease, or atrial septal defect had right heart catheterization, contrast RV angiography, and/or radionuclide RV angiography. The "A" wave was absent in the 31 patients with atrial fibrillation. When normalized for body surface area, end diastolic IVC dimension correlated with RA pressure ($R=0.72$, $P\leq 0.001$). An "A" wave $\geq$125% end diastolic IVC dimension occurred in 9 of 12 patients with RV end diastolic pressure $\geq$10mmHg, but in none <10mmHg ($P<0.001$). A "V" wave$\geq$140% end diastolic IVC dimension occurred in 8 of 11 patients with significant tricuspid insufficiency, but in no patient with mild or no tricuspid insufficiency ($P\leq 0.001$). Lack of respiratory variation in end diastolic IVC dimension occurred in severe RV dysfunction (radionuclide RV ejection fraction <25%); inspiratory decrease of IVC dimension correlated with RV ejection fraction ($R=0.75$, $P<0.001$). We conclude that echocardiographic assessment of IVC size and pulsation is an important index of right heart function: (1)IVC size correlates with RA pressure, (2) a large "A" wave predicts a high RV end diastolic pressure, (3) a large "V" wave predicts significant tricuspid insufficiency, and (4) lack of respiratory variation in IVC size predicts severe RV dusfunction.

WEDNESDAY, MARCH 18, 1981
AM
NUCLEAR CARDIOLOGY: EVALUATION OF CARDIAC FUNCTION
10:30-12:00

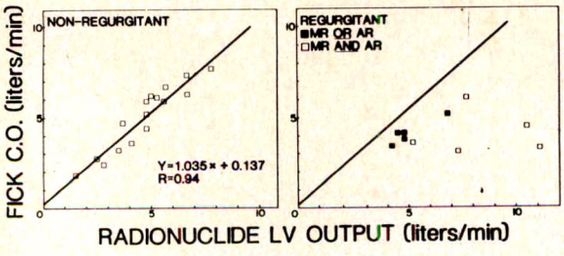
DIRECT MEASUREMENT OF CARDIAC OUTPUT BY GATED EQUILIBRIUM BLOOD POOL SCINTIGRAPHY. G.J. Dehmer, MD, B.G. Firth, MD, S.E. Lewis, MD, J.T. Willerson, MD,FACC, L.D. Hillis, MD, FACC, U of Texas Health Science Center, Dallas, TX

We have previously described a non-geometric technique for the determination of LV volumes from the count data derived from gated equilibrium blood pool scans (GS) and have validated this technique by demonstrating an excellent correlation between scintigraphically and angiographically-determined LV volumes. To provide further prospective evaluation of this method and to validate its ability to determine stroke volume (SV) and cardiac output (CO) by a technique independent of geometric assumptions, simultaneous measurement of CO by thermodilution (THD) technique and GS was performed in 21 patients (pts) without valvular regurgitation or intracardiac shunting. During an imaging period of 6-8 mins, CO was measured by THD every 1½ mins, and the average of 3-5 THD COs was correlated with the GS CO (obtained by multiplying heart rate by the derived SV {end-diastolic volume minus end-systolic volume}). To validate further the reliability of GS measurements at high COs, 7 pts had multiple measurements of CO at rest and during isoproterenol infusion (1-4 micrograms/min). There was an excellent correlation between THD and GS CO (GS CO = 0.99 THD CO - 0.005 L/min; n=31, SEE=0.175 L, r=0.97) as well as between THD and GS SV (GS SV = 1.03 THD SV - 2.8 ml; n=31, SEE=2.5 ml, r=0.95). In addition, the correlation between GS and angiographic measurements of LV volumes continued to be excellent: in 15 pts with technically adequate angiograms, GS LV volume = 0.90 (Angiographic LV volume) + 7 ml; n=30, SEE=10 ml, r=0.91. Thus, this study further validates the non-geometric method of measuring LV volumes by gated scintigraphy and demonstrates its ability to measure LV stroke volume and cardiac output reliably.

QUANTITATION OF LEFT VENTRICULAR OUTPUT IN PATIENTS WITH AND WITHOUT LEFT-SIDED VALVULAR REGURGITATION USING EQUILIBRIUM RADIONUCLIDE VENTRICULOGRAPHY

Marvin A. Konstam, MD; Joshua Wynne, MD, FACC; B. Leonard Holman, MD, FACC; Edward J. Brown, MD; Jane M. Neill; Joseph F. Kozlowski, Harvard Medical School and Brigham and Women's Hospital, Boston, MA

We examined the accuracy with which LV output can be estimated by radionuclide ventriculography. Following in vivo red blood cell labeling, we measured LV end-diastolic and end-systolic count rates and the count rate in 5 ml of patient's blood. After estimating the average ratio of counting efficiency for the LV to counting efficiency for the blood sample (E_{LV}/E_S) in 6 patients, we calculated LV output in 26 other patients as LV activity ejected per minute (min) divided by activity per liter of blood divided by the previously estimated E_{LV}/E_S. Radionuclide LV output closely approximated Fick CO (r = 0.94) in patients without mitral or aortic regurgitation (MR or AR) and exceeded Fick CO in all patients with MR or AR. The radionuclide ventriculogram is an excellent means for noninvasive estimation of LV output.



ONE MINUTE MULTIPLE GATED EQUILIBRIUM SCINTIGRAPHY FOR ASSESSMENT OF LEFT VENTRICULAR EJECTION FRACTION AND SEGMENTAL WALL MOTION: VALIDATION WITH STATE OF THE ART INSTRUMENTATION AND OPTIMIZED SPACE-TIME SMOOTHING

Ronald Levy, MD; Alan Rozanski, MD; David Brown, RT; Ken Van Train, RT; Ernest Garcia, PhD; Nancy Pantaleo , RN; Jamshid Maddahi, MD; Alan Waxman, MD; and Daniel Berman, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, Ca.

Due to patient (pt) difficulty in sustaining peak bicycle exercise, shortened data acquisition time during multiple gated equilibrium scintigraphy (MGES) is desirable. Thus, in 14 consecutive pts undergoing MGES, we determined whether state-of-the-art instrumentation, including use of a camera with a ¼ inch crystal and high fidelity computer video display, and enhanced image processing permit the accurate assessment of LV ejection fraction (EF) and segmental wall motion (SWM) from data collected over only 1 minute (min). Following acquisition of consecutive 1, 2, and 1 min images in the 45° LAO view, an optimized space-time smoothing algorithm was applied. LVEF's were determined in a blinded fashion by an experienced operator, using light pen assignment of the LV and background regions. A second operator determined LVEFs on the first 1 min study. SWM was separately evaluated by 2 blinded observers using a 5 point scoring system (3=normal, -1=dyskinesis). Differences >1 were considered disagreement. A high correlation was found between 1 and 2 min LVEFs (r=.86). Intraobserver agreement of 1 min LVEFs was also high (r=.89), as was interobserver agreement (r=.91). With respect to SWM, 92% agreement for 1 and 2 min studies and 99% agreement for consecutive 1 min studies was found. Interobserver agreement for SWM was 98% in 1 min studies. Thus, with recent technical advances, it is possible to accurately assess LVEF and SWM from 1 min multiple gated scintigraphic studies. This improvement should enhance evaluation of LV performance during peak bicycle exercise.

RADIONUCLIDE DETERMINATION OF LEFT VENTRICULAR VOLUME: COMPARISON OF COUNTS-BASED AND GEOMETRIC METHODS.

Barry Massie, MD, FACC and Barry Kramer, MD. VA Hospital and University of California, San Francisco, CA.

Recently, several methods have been proposed for the scintigraphic determination of left ventricular (LV) volume. To compare their accuracy, we measured LV volume by: 1) LAO COUNTS: a counts-based method employing left anterior oblique (LAO) blood pool scintigrams and an externally counted blood sample reference; 2) RAO GEOM: a geometric method employing measured long and short axes from first pass right anterior oblique (RAO) scintigrams and a calibrated reference grid; 3) BIPLANE GEOM: a geometric method using measured long and short axes from the first pass RAO scintigram and a second short axis from the LAO blood pool study. A single crystal gamma camera and commercially available analysis system were utilized. The radionuclide findings were correlated with RAO area-length volumes from LV angiography performed within 48 hours in 18 patients whose end-diastolic and end-systolic volumes (EDV and ESV) ranged from 89-328 and 12-161 ml, respectively.

	LAO COUNTS		RAO GEOM		BIPLANE GEOM	
	R	SEE	R	SEE	R	SEE
EDV	.96	17	.85	35	.88	29
ESV	.95	15	.91	20	.88	25
Combined	.98	16	.93	26	.94	24

R=correlation coef.; SEE=std. error of estimate (ml)

While all 3 methods yielded highly significant correlations for EDV, ESV and both volumes together ($p<.001$ for each), the LAO counts-based method was clearly superior. Since this method also allows multiple determinations following the administration of a single dose of radioactivity (such as at rest and with exercise or pre and post-intervention), we conclude that it is the method of choice for measurement of LV volumes.

THE DETECTION OF ABNORMAL PULMONARY CAPILLARY WEDGE PRESSURE FROM THE DISTRIBUTION OF REGIONAL PULMONARY BLOOD VOLUME ON THE GATED BLOOD POOL SCAN

Adalberto Urbina, MD; Robert D. Okada, MD, FACC; Mary D. Osbakken, MD; Charles A. Boucher, MD, FACC; Gerald M. Pohost, MD, FACC; H. William Strauss, MD, FACC; Igor Palacios, MD, Massachusetts General Hospital, Boston, MA

To determine if the apex-to-base relative distribution of pulmonary blood volume obtained from gated blood pool scans could be used as a noninvasive method to estimate pulmonary capillary wedge pressure (PCWP), 77 patients had PCWP determination at cardiac catheterization and gated blood pool scans within 15 days of catheterization (47% within 24 hours, including 10 simultaneous measurements). The relative distribution of pulmonary blood volume at the apex and base of the lung was determined from the end-systolic left anterior oblique view frame by placing equal-sized regions-of-interest over the right lung. Apex counts divided by base counts (A/B ratio) was considered abnormal if >1. Ejection fraction (EF) was also calculated from the gated blood pool scan and considered abnormal if <45%. The PCWP was considered normal if ≤12 mm Hg and abnormal if >12 mm Hg.

	A/B Ratio			EF	
	Normal	Abnormal		Normal	Abnormal
PCWP			PCWP		
Abnormal	5	21	Abnormal	9	17
Normal	45	6	Normal	32	19

The sensitivities of the A/B ratio and EF for an abnormal PCWP were 80% and 65% respectively, and the specificities 88% and 62%. These data suggest that the A/B ratio can be reliably used to differentiate normal from abnormal PCWP.

CORRELATION OF CINEANGIOGRAPHY AND BLOOD POOL SCAN FOR MEASUREMENT OF LEFT VENTRICULAR VOLUME IN HUMAN CADAVER HEARTS

Igor Palacios, MD; Mark R. Goldman, MD, FACC; Thomas Aretz, MD; Charles A. Boucher, MD, FACC; Robert D. Okada, MD, FACC; Mary D. Osbakken, MD, PhD; John Newell; Marsha Leavitt, Peter C. Block, MD, FACC, Massachusetts General Hospital, Boston, MA

The area-length method is widely used in the determination of left ventricular volume (LVV). Although previous studies have reported that this technique overestimates the true volume (TV), it is unknown whether this overestimation is the same at different volumes. In the present study using 10 post-mortem hearts, LVV were determined by both biplane right and left anterior oblique (RAO-LAO) cine ventriculography (LVA) and biplane RAO-LAO Technetium blood pool scans (LVR) and the results were correlated with TV. LV was made water tight by suturing the mitral valve leaflets, cross clamping the aortic root at the level of the aortic valve and ligation of the coronary ostia. Increases in LVV (10-150 ml) were obtained in each heart by step wise increments of known amounts of contrast material mixed with 99m Technetium injected through a cannula placed in the LV apex. Both LVA and LVR were determined at each volume. LVA correlated well with TV (R = 0.98). LVR correlated well with TV (R = 0.97). LVR correlated well with LVA (R = 0.96). Both techniques resulted in overestimation of TV with an upward shift of the regression line of 37.3 ml ± 10 (SEM) for LVA and 23.6 ml for LVR. The percent overestimation error was significantly greater at smaller LVV (error = 33% at TV = 30 ml and 10% at TV = 100 ml, $p<0.001$). Thus: (1) the percent error in the determination of LVV is proportional to 1/TV and (2) LVV can be reliably obtained from both LVR and LVA using the area-length method.

WEDNESDAY, MARCH 18, 1981
AM
PLATELET ACTIVITY AND INHIBITION: EXPERIMENTAL AND CLINICAL OBSERVATIONS
10:30-12:00

FAILURE OF ASPIRIN TO PREVENT INCORPORATION OF INDIUM LABELLED PLATELETS INTO CARDIAC THROMBI IN MAN

A. Chadwick Cox, PhD; Michael D. Ezekowitz, MD, FACC, University of Oklahoma Health Sciences Center, Oklahoma City, Okla.

The purpose of this investigation was to study in vivo and in vitro platelet function in aspirin and non-aspirin treated patients with cardiac thrombi. In vitro function was tested by examining the aggregation response of platelets to ADP (1.6 μg/ml) and collagen (2 μg/ml); in vivo function, by examining the incorporation of Indium-111 labelled platelets into cardiac thrombi using gamma camera imaging. Eight patients with left ventricular aneurysms and mural thrombi were studied. Four patients were treated with aspirin in doses of 300 to 1200 mg/day. The remaining 4 patients were non-aspirin treated controls. Prior to Indium labelling of platelets, the aspirin dose significantly reduced the average percent total aggregation induced by collagen and ADP ($P<.02$); 54 and 76% aggregation for control group versus 29 and 67% for aspirin group. Most of this aggregability was retained after Indium-111 labelling as was the significant differences between the groups; 53 and 68% for the control group and 17 and 54% for the aspirin group. The autologous labelled platelets were incorporated into ventricular thrombi in all patients as evidenced by Indium-111 scintigraphy. We conclude that in spite of demonstrating the expected inhibitory effect of aspirin on platelet aggregation, these aspirin impaired platelets participated in active cardiac thrombosis in vivo.

EFFECT OF IBUPROFEN ON PLATELET DEPOSITION IN GORE-TEX AND AUTOLOGOUS VEIN GRAFTS

Kevin R. Kopesky, BA; Mrinal K. Dewanjee, PhD; Meng F. Lim, BS; Michael P. Kaye, MD, FACC, Mayo Clinic and Foundation, Rochester, MN

To quantitatively study platelet deposition on arterial prostheses and the effect of platelet inhibitory therapy with ibuprofen, 22 dogs underwent bilateral femoral artery grafting with one polytetrafluoroethylene (Gore-Tex) and one autologous vein graft. Seven dogs received 12.5 mg/kg ibuprofen intravenously, 15 minutes prior to arterial clamping; 6 dogs 400 mg orally every 8 hours for 48 hours, last dose 2 hours preop; and 9 dogs were untreated. Using autologous indium-111-labeled platelets injected 12 hours prior to operation as a platelet marker, grafts were removed 1 hour following resumption of blood flow. Radioactivity per unit weight was determined and compared with radioactivity per unit weight of blood. Synthetic and autologous grafts were then compared.

	Gore-Tex/ Blood	Vein/ Blood	Gore-Tex/ Vein
Control	19.70±5.40	3.02±1.77	11.20±4.11
IV Ibuprofen	1.48±0.72	1.09±0.57	1.70±1.32
Oral Ibuprofen	1.30±0.51	1.06±0.43	1.63±1.06

Ibuprofen treated dogs (IV and oral) had a 12-fold reduction in platelet deposition on Gore-Tex grafts and a 3-fold reduction on venous grafts. Platelet deposition was reduced significantly in Gore-Tex grafts ($P<0.001$) to a level comparable to that in autologous veins.

PLATELET THROMBUS FORMATION IN STENOSED CANINE CORONARY ARTERIES AND THEIR INHIBITION WITH IBUPROFEN

John D. Folts, Ph. D.; Frank C. Bonebrake, BS; and Brian Bertha, Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin.

We have previously shown that platelet thrombi periodically form in mechanically stenosed dog circumflex (Circ) coronary arteries producing cyclical reductions in coronary flow (CRF) as measured with EMF flowmeter. In 17 open chest anesthetized dogs given a 70% stenosis of the circ, (which just abolishes the reactive hyperemic response (RH) to a 20 second complete occlusion), CRF occurred with an abrupt return to control levels. The CRF were reduced with 10 mg/kg and abolished with 15 mg/kg of Ibuprofen (I) (Motrin^{R}) IV. The CRF gradually returned after 30 to 45 minutes. Heart rate decreased from 113 $\pm$ 15 to 91 $\pm$ 19 beats/minute ($p < .01$) and in vitro platelet aggregation using ADP as the stimulus decreased from 63 $\pm$ 13 to 40 $\pm$ 7 light transmission units ($p < .01$) with the 15 mg/kg of I. Plasma epinephrine (E) = 574 $\pm$ 149 pgm/ml and norepinephrine (NE) = 197 $\pm$ 62 pgm/ml before, and E = 259 $\pm$ 103 pgm/ml ($p < .01$) and NE = 138 $\pm$ 46 pgm/ml ($p < .05$) after the larger dose of I. We postulate that I temporarily inhibits prostaglandin synthesis, and subsequent platelet aggregation. The I lowers plasma E and NE and also heart rate, possibly by inhibiting prostaglandin synthesis in the adrenal medulla. With the reduced heart rate there was a small return of RH. We further postulate that the reduction in heart rate, plasma E and NE along with inhibition of CRF, if it occurs in man, would be beneficial to patients with coronary artery disease.

CONSISTENT PLATELET ACTIVATION ASSOCIATED WITH EARLY RECURRENT MYOCARDIAL INFARCTION

Alon Marmor, MD; William Schillizzi; Burton E. Sobel, MD, FACC; and Robert Roberts, MD, FACC, Washington University, St. Louis, Missouri

We have recently shown that patients with subendocardial myocardial infarction (MI) have a high incidence (43%, n=58) of early recurrent infarction (ERI) within 14 days, manifested by re-elevation of plasma MB CK, serum myoglobin and by new left ventricular wall motion abnormalities. In the present study participation of platelets in this process was evaluated by serial studies of these parameters coupled with prospective, serial assays of platelet factor IV (PF IV), an index of platelet degranulation. Blood samples were obtained for 14 days at intervals of every 4 hr for 3 days and every 12 hr for the subsequent 11 days beginning at the time of admission for MI. If ERI was suspected clinically, sampling frequency was increased again to 4 hr intervals. Samples were analyzed for PF IV by radioimmunoassay. Values in normal subjects (n=10) and in patients with coronary disease without concurrent infarction (n=15) averaged 7 $\pm$ 1 (SD) and 14 $\pm$ 6 ng/ml, respectively with a coefficient of variation of <10%. All patients exhibited increased PF IV with the initial MI (>100 ng/ml), with a return of values to normal within 48 hr in every case. Each episode of documented ERI was temporally associated with re-elevation of PF IV (average peak re-elevation = 40 $\pm$ 10). The PF IV was always elevated in the first sample temporally associated with ERI. Although it is not yet clear whether the platelet factor IV elevations actually preceded the onset of cell death associated with ERI, it is clear from these data that platelet activation is a consistent and temporally associated concomitant of reinfarction and hence a potential contributor to the additional myocardial injury.

RED CELL INVOLVEMENT IN PLATELET THROMBI FORMED IN STENOSED CANINE CORONARY ARTERIES

John D. Folts, Ph.D., Al R. Kutchera, M.S., Frank C. Bonebrake, Brian G. Bertha, Kennedy W. Gilchrist, M.D. The University of Wisconsin Medical School, Madison, WI.

Platelet thrombi (Th) form every 5-15 minutes in mechanically stenosed dog circumflex coronary arteries producing cyclical reductions in blood flow, measured with (EMF) which can lead to acute myocardial ischemia and sudden death. To collect the Th to determine the morphology and composition of Th after heparinization, a silastic rubber "T" tube (T) was placed distal to the stenosis (S) and in line with the normal circumflex flow pattern. The side arm is clamped and blood flows through the S, T, and into the distal circumflex bed until a platelet thrombus forms. Then the distal side of the T tube is clamped and the side arm unclamped, diverting the blood flow coming through the stenosis, through the side arm, into a beaker of fixative, thus, collecting the Th. The collection is repeated many times in each dog. In 7 dogs a Th was collected every time the flow declined. The Th was prepared for light and scanning electron microscopy. On high magnification using Carstairs stain and fluoresceine conjugated antisera, fused platelets and red cells (RBCS), both intact and ruptured, are noted at the edges of Th. We postulate that turbulent blood flow or packing of RBCS proximal to, and in S, damages some RBCS, releasing RBCS' ADP which enhances platelet aggregation which in turn releases substances that lyse more RBCS. Thus a self-perpetuating Th formation mechanism may develop. This may also occur in man where RBCS may accumulate and may be packed together proximal to a tight coronary arterial stenosis leading to release of ADP from lysed RBCS, increased platelet thrombus formation, acute ischemia and sudden death.

PLATELET ACTIVITY IN CORONARY DISEASE , RELATIONSHIP TO SMOKING AND HYPERLIPIDEMIA .

Charles w. Pumphrey M.R.C.P. National Heart Hospital, London W1 U.K. Joan Dawes Ph.D. M.R.C. Radioimmunoassay Team, Edinburgh,Scotland.

Platelets cause both atherosclerosis and acute arterial thrombosis. It is uncertain whether the coronary risk factors activate platelets to cause accelerated atherosclerosis, or whether any increased platelet activity is secondary to established arterial disease. We have measured the plasma level of the platelet-specific protein beta-thromboglobulin (BTG) which is thought to reflect platelet activity and is constant in the clinical steady state. In a control group there is no difference in plasma BTG between smokers (31.8 $\pm$ 1.6 ng/ml n = 45) and non smokers (32.2 $\pm$ 1.2 ng/ml n = 56). Asymptomatic patients with hyperlipidemia had a similar BTG (32.8 $\pm$ 1.7 ng/ml n = 32). However patients with symptoms of ischaemic heart disease have a significantly elevated plasma BTG (40.7 $\pm$ 1.4 n = 104, $P < 0.01$). Patients with two or more risk factors have a significantly higher BTG (45.2 $\pm$ 2.2 ng/ml n = 47) than those with one or no identified risk factor present (37.1 $\pm$ 1.7 ng/ml n = 57, $P < 0.005$). We conclude that neither smoking nor the present of hyperlipidemia increase platelet activity. However patients with coronary disease have platelets activated by the established arterial disease, and the increased activity seen in patients with more risk factors is due to the presence of more extensive disease.

WEDNESDAY, MARCH 18, 1981
AM
PEDIATRIC CARDIOLOGY—NON-INVASIVE STUDIES
10:30-12:00

PROSPECTIVE DIAGNOSIS OF CONOTRUNCAL MALFORMATIONS IN INFANTS USING SUBXIPHOID TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Stephen P. Sanders, MD, Fredrick Z. Bierman, MD, Roberta G. Williams, MD, Children's Hospital Medical Center, Boston, MA. 02115

Subxiphoid two-dimensional echocardiography (S2DE) was successfully performed and interpreted prospectively in 90 of 94 infants, ages one day to 12 months (median - 21 days), with conotruncal malformations and d-ventricular loop proved at cardiac catheterization over a 17 month interval.

Eighty-nine of 90 patients (pts) (99%) were correctly included in the category of conotruncal malformations, and in 85 pts (94%) the specific lesion was correctly diagnosed. All 37 pts with d-transposition of the great arteries were correctly diagnosed based on great artery morphology and direct visualization of ventriculo-arterial connections. Nine of ten pts with double-outlet RV were recognized by the origin of at least "1½" great arteries from the RV. In the tenth pt a large main PA and patent ductus arteriosus were mistaken for the aortic arch. Tetralogy of Fallot (TOF) was correctly diagnosed in 29 of 31 pts and TOF with pulmonary atresia in 6 of 6 pts. Continuity between the RV and PA, with infundibular narrowing, was seen in all pts diagnosed as TOF, while discontinuity between the RV and PA characterized TOF with pulmonary atresia. Two pts with TOF were incorrectly diagnosed by S2DE: one as a large membranous ventricular septal defect, and one as TOF with pulmonary atresia. Five of six pts with truncus arteriosus communis were correctly diagnosed by demonstrating continuity between the PA's and the ascending portion of the truncus arteriosus. Limited examination of the sixth pt lead to the incorrect diagnosis of double-outlet RV.

By direct visualization of ventricular and conotruncal anatomy, S2DE permits accurate diagnosis of conotruncal malformations in infants.

THE USE OF FETAL ECHOCARDIOGRAPHY IN THE DIAGNOSIS AND MANAGEMENT OF ANTENATAL ARRHYTHMIAS

Charles S. Kleinman, MD; John C. Hobbins, MD; Diana C. Lynch; Richard Donnerstein, MD; C. Carl Jaffe, MD; Norman S. Talner, MD, Yale University School of Medicine, New Haven, CT

M-mode fetal echocardiography has been used to analyze the cardiac rhythms of 28 fetuses (24-40 weeks (wks) gestation) referred for evaluation of prenatal arrhythmias. Arrhythmias were documented in 23 (82%) cases. Heart rate, atrioventricular (A-V) contraction sequence, mitral valve motion, and postectopic pauses were studied. Atrial premature beats (APB's) were diagnosed in 14 cases (61%). The APB's had ceased in 9 at restudy later in gestation. In the remaining 5 cases APB's were noted at birth but resolved by the third day. Six fetuses had brief episodes of regular bradycardia which resolved later in pregnancy. Atrial flutter with varying A-V block and congestive heart failure (CHF) was diagnosed in one fetus at 38 weeks. Caesarian delivery and electrical cardioversion successfully treated this child. Severe CHF and paroxysmal supraventricular tachycardia were diagnosed immediately prior to the stillbirth of a hydropic infant. Complete A-V block was diagnosed in a 24 wk fetus. Fetal echocardiography may contribute to the diagnosis and management of fetal cardiac arrhythmias.

PULMONARY VALVE ATRESIA: DIAGNOSIS BY PULSE DOPPLER/ TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Joan C. Korfhagen, B.A., RDMS, Richard A. Meyer, M.D., FACC, Samuel Kaplan, M.D., FACC, Children's Hospital Medical Center, Cincinnati, Ohio.

Pulmonary valve atresia with an intact ventricular septum (PA) constitutes a medical emergency in the newborn period. Prompt recognition and treatment of this ductal dependent lesion is crucial for the survival of these very fragile babies. With two-dimensional (2-D) echocardiography the pulmonary valve and right ventricle (RV), can be visualized. It is not possible with 2-D alone to determine whether there is complete obstruction to pulmonary flow. With combined pulsed Doppler and two-dimensional echocardiography (Dop-2D) flow through the right ventricular outflow tract (RVOT) and across the pulmonary valve can be assessed. Therefore 8 newborns with documented PA were evaluated by Dop-2D and compared to patients with pulmonary stenosis (PS) and normal RVOT. All patients with PA exhibited characteristically absent flow in the RV and RVOT. In addition the size of the RV and RVOT were estimated. Once the Doppler sample volume was beyond the valve a typical Doppler signal of continuous flow from a patent ductus arteriosus was detected. These patterns differed markedly from patients with severe PS or unobstructed RVOT. It now appears possible to accurately distinguish PA from PS at the bedside and greatly facilitate the management of these critically ill infants. We suggest that as our experience broadens using this technique, cardiac catheterization may be obviated, permitting immediate surgical intervention, and enhance the survival of these newborns.

CARDIAC INVOLVEMENT WITH KAWASAKI DISEASE IN CHILDREN FROM NEW ENGLAND

Kyung J. Chung, MD, FACC; Robert E. Rinaldi, MD; David R. Fulton, MD; Marshall B. Kreidberg, MD, FACC, Tufts University School of Medicine, Boston, Massachusetts.

Thirty seven patients (pts), ages 6 months to 11 years, meeting clinical criteria for Kawasaki Disease (KD) were studied prospectively during April-July, 1980. There were 23 males and 14 females. All but 4 pts were white (2 blacks, 1 oriental, 1 Indian). A protocol was designed for evaluation of cardiac involvement including ECG, cardiac enzymes, M-mode (Echo) and 2-dimensional (2-DE) echocardiogram. ASA (100 mg/kg/day) was given during the febrile period followed by 30 mg/kg/day for 10 weeks or longer if platelet counts were elevated. Angiocardiography to delineate coronary artery (CA) and LV asynergy was performed 2 months after onset of KD. Seventeen (46%) pts had abnormal Echo findings during acute phase; flat or decreased ventricular septal motion in 9, pericardial effusion in 6 and congestive heart failure (CHF) in 5 manifested by chamber dilatation, decreased shortening fraction and prolonged systolic time interval. Abnormal Echo findings returned to normal in 2-4 weeks except in 2 pts who continued to show CHF. Four pts (11%), all of whom had abnormal acute stage Echo, showed CA disease on 2-DE by 2 weeks after onset of KD. Three had coronary aneurysms and 1 had dilated CA. Of 28 pts undergoing angiographic study, 24 showed normal LV and CA anatomy. Three pts had coronary aneurysms and 1 had dilated CA with LV asynergy. All were accurately diagnosed by 2-DE. On the basis of our study, serial M-mode and 2-D echocardiograms were sufficient to rule out cardiac involvement in KD. Those who have abnormal echoes should have angiocardiography to further delineate cardiac pathology.

COMPUTERIZED AXIAL TOMOGRAPHY OF THE THORAX: SIZE OF RIGHT PULMONARY ARTERY IN RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION

Carol M. Cottrill, M.D., FACC, Gregory L. Johnson, M.D., FACC, Jacqueline A. Noonan, M.D., FACC, University of Kentucky, Lexington, Kentucky

Computerized Axial Tomography (CAT) scans of the thorax were performed in 22 children ranging in age from 7 weeks to 14 years (mean = 3.5 years) who weighed 6 pounds to 86 pounds (mean = 28 pounds). The children had these cardiac lesions:

16 Tetralogy of Fallot (TOF), one post-op shunt
1 Pulmonary atresia with Intact Septum, post-op shunt
1 Complex RVOT Obstruction
1 Idiopathic Pulmonary Hypertension
3 No heart disease (NHD)

Structures were identified as follows: right pulmonary artery (RPA) 21/22, superior vena cava 21/22, right mainstem bronchus (RMB) 21/22, descending aorta 17/22, ascending aorta 10/22. These were measured and ratio of RPA diameter to RMB diameter was determined:

NHD	1.5 - 1.7
RVOT Obstruction - no shunts	< 1.5
RVOT Obstruction - with shunts	> 1.8
Pulmonary Hypertension	> 1.8

CAT scanning permits identification and measurement of RPA. This information may help plan surgical intervention.

WEDNESDAY, MARCH 18, 1981
AM
MYOCARDIAL INFARCTION—A CLINICAL PATHOLOGIC SPECTRUM
10:30-12:00

RIGHT VENTRICULAR INFARCTION : CLINICAL COURSE AND FOLLOW-UP.

Victor Legrand, MD, Jean-Pierre Smeets, MD, Jean-Claude Demoulin, MD, Pierre Rigo, MD, Henri E. Kulbertus, MD, FACC, Section of Cardiology. University of Liège, Belgium.

Of 146 consecutive patients with inferior wall myocardial infarction (IWMI) submitted to Tc 99 m pyrophosphate scintigraphy, 34 (23 %) had concomitant right ventricular infarction (RVI) diagnosed by right ventricular Tc uptake. Gated blood pool scans (GBPS) performed in 14 cases showed right ventricular abnormalities in 12 (right ventricular asynergy : 8 ; right ventricular dilatation : 7 ; decreased right ventricular ejection fraction : 10).
Complications were common in the acute stage. Shock was noted in 14 cases, atrial fibrillation in 6, ventricular fibrillation in 6 and severe atrio-ventricular conduction disorders in 10. In-hospital mortality however was low (2 cases ; 5,9 %).
All patients were followed up for one year. 5 additional deaths occurred during follow-up (2 from cardiac failure ; 2 from recurrent MI, 1 from pulmonary embolism). Repeat GBPS at 3 months showed improved right ventricular ejection fraction and size in all but one of 12 cases. However, all 4 patients with large right ventricular infarction as judged from Tc 99 m pyrophosphate scintigraphy still had right ventricular enlargement and decreased right ventricular ejection fraction. Among 8 cases with smaller right ventricular infarction, only 2 still showed altered right ventricular function at 3 months.
Conclusions : 1) In spite of frequent complications in the acute stage, patients with right ventricular infarction have an overall good prognosis and long term outcome ; 2) those with extensive scintigraphic right ventricular lesions have more impressive and longer lasting hemodynamic disturbances.

RADIONUCLIDE EVALUATION OF RV AND LV FUNCTION (FX) IN CHILDREN-CINEANGIOGRAPHIC VALIDATION AND OBSERVATIONS IN TRANSPOSITION OF THE GREAT ARTERIES (TGA)

M.D. Parrish, MD, T.P. Graham, Jr.,MD, FACC, M.L. Born,MD, F.D. Rollo, MD, J. Weinberger, RN, O.H. Wolfe: Vanderbilt Univ. Med. CTR., Nashville, Tennessee 37232

Validation of an equilibrium radionuclide technique for assessment of RV and LV FX has not been reported in children with congenital heart disease (CHD). We performed resting equilibrium radionuclide ventriculograms (RVG's) in 19 children with diverse types of CHD (ages 4-19,mean 10yr), with exercise RVG's in 15 of the children. Cardiac catheterization (cath) was performed in 11 of 19 children within 2 weeks of RVG. Resting LV and RV ejection fractions (EF) from RVG and cath were compared by linear regression analysis: RVEF (cath vs RVG) r=0.83, S.E.E. 0.08, LVEF r= 0.88, S.E.E. 0.06, RVEF (TGA pts only) r= 0.98, S.E.E. 0.03. Inter observer correlations for RV and LV EF were 0.81and 0.98 respectively. With exercise, the interobserver correlations for RV and LV were 0.91and 0.93. Five pts with TGA had exercise studies: 2 with congenitally corrected TGA (CCTGA) and 3 with a mustard repair. The three TGA pts were all asymptomatic but only one had a normal increase in RVEF with exercise (0.53 to 0.78). One 18yr old with CCTGA with VSD, pulmonary stenosis and a Blalock-Taussig shunt had a normal exercise response, while an 11yr old with CCTGA and severe tricuspid incompetence had a fall in RVEF with peak exercise. We conclude that RV and LV EFs showed good correlations with cath EF's. Furthermore, we were able to perform this study in exercising children with no deterioration in inter-observer correlations. These techniques can provide important information regarding systemic ventricular FX in TGA, and aid in the long term evaluation of current methods of treatment for TGA and CCTGA.

SERIAL EVALUATION OF RIGHT VENTRICULAR FUNCTION AFTER RIGHT VENTRICULAR INFARCTION.

Tsunehiro Yasuda, MD; Robert Okada, MD, FACC; John B. Bingham, MB; Herman K. Gold, MD, FACC; Robert C. Leinbach, MD, FACC; Gerald M. Pohost, MD, FACC; H. William Strauss, MD, FACC, Massachusetts General Hospital, Boston, MA.

To define the course of right ventricular function after right ventricular myocardial infarction (MI), 61 patients with acute MI were studied initially within 18 hours after chest pain with multi-gated blood pool scans. Follow-up studies were performed at 90 minutes, 10 days and 3 months. In addition, symptom limited supine bicycle exercise was performed at 3 months post RV MI. Twenty of the 61 patients had abnormal RV regional wall motion on the initial multi-gated blood pool scan and were considered to have RV MI. The RV ejection fraction (EF) results are (mean ± 1 SD):

TIME	RVEF	
1) Initial	33.2 ± 13.0	p<.05
2) 90 minute	35.0 ± 14.6	
3) 10 days	45.7 ± 11.3	
4) 3 months	41.0 ± 16.6	
5) Pre-exercise	39.1 ± 8.82	
6) Maximum exercise	39.5 ± 12.0	

These data show that (1) RVEF improves within the first 10 days following RV MI, (2) There is no significant further improvement in RVEF 10 days to 3 months following RV MI, (3) Despite the early improvement in RVEF following RV MI, RV function was still abnormal at 3 months as demonstrated by a failure to increase RVEF with exercise.

NON TRANSMURAL (SUBENDOCARDIAL) MYOCARDIAL INFARCTION IN MAN: THE PREVALENCE OF TOTAL CORONARY OCCLUSION.
Marcus A. DeWood,M.D; Julie Spores,CRNA; Robert N. Notske, M.D,FACC; J. Paul Shields,M.D,FACC; Carroll Simpson,M.D, FACC; Samuel Selinger,M.D; William E. Shell,M.D.
Sacred Heart and Deaconess Medical Centers, Spokane, WA.

Total coronary occlusion is a frequent finding in transmural myocardial infarction. However, knowledge concerning the prevalence of total coronary occlusion during nontransmural myocardial infarction (NMI) has been acquired mostly from autopsy data. Few studies describe the occurrence of total coronary occlusion during NMI in patients (pts). From mid 1976 to mid 1980, 152 pts underwent left ventriculography and coronary arteriography (CA) within 96H of symptom onset of NMI characterized by substernal chest pain associated with 1) ST-T wave abnormalities not progressing to pathologic Q waves and 2) abnormal elevation of total CK activity prior to any intervention. The 152 pts were then grouped by subsets reflecting the time interval in hours (H) from peak symptoms to investigation by CA. Overall, the prevalance of total occlusion by CA was 44/152 (28.9%). Analysis of subsets indicated the following. *p=NS

0-24H	24-48H	48-72H	72-96H
18/88 (20.4%) *	11/31 (35.4%) *	9/21 (42.8%) *	6/12 (50%)

No pt had normal coronary arteries by CA. These data suggest 1) total coronary occlusion is infrequent in early nontransmural MI in man, 2) the prevalance of total occlusion appears to increase in pt groups over discrete time intervals and 3) severe alterations in coronary tone in conjunction with preexisting atherosclerotic plaque as opposed to total occlusion may be contributory to oxygen deprivation in early NMI.

TWO-DIMENSIONAL ECHOCARDIOGRAPHIC RECOGNITION OF SURGICALLY REMEDIABLE COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION
Gary S. Mintz MD, FACC, Mark F. Victor MD, Morris N. Kotler MD, FACC, Wayne R. Parry, Bernard L. Segal MD, FACC
Cardiovascular Institute, Hahnemann Medical College, Philadelphia, Pennsylvania

The appearance of a new systolic murmur in a patient (PT) with congestive heart failure following myocardial infarction suggests the presence of a surgically remediable structural defect. Survival depends on rapid accurate diagnosis leading to prompt definitive therapy. Using real-time two-dimensional echocardiography (2D-E) we studied 13 PTS who presented in this manner 3 days to 6 weeks after infarction. Four PTS had a ruptured papillary muscle (PM); 2D-E findings were a flail mitral leaflet with a mass attached by chordae to the tip of the leaflet and a truncated PM. All had severe angiographic mitral insufficiency and surgical confirmation of PM rupture. Five PTS had acute irreversible PM dysfunction. 2D-E showed increased density and immobility of the PM and dyskinetic LV wall motion involving and displacing the base of the PM. One of the mitral leaflets was retracted toward the LV apex. All PTS with acute PM dysfunction had severe angiographic mitral insufficiency and surgical confirmation of intact PM. Four PTS had a ventricular septal defect; 2D-E showed a localized septal aneurysm with a defect in septal continuity. At catheterization all had a large left-to-right shunt; 3 PTS had surgical confirmation of septal rupture (1 PT refused surgery).

We conclude: 2D-E is useful in studying PTS with a new systolic murmur and heart failure following myocardial infarction to detect remediable structural defects. Rapid diagnosis may lead to enhanced survival in these patients.

THE NONTRANSMURAL VS TRANSMURAL MYOCARDIAL INFARCTION: IS THERE A DIFFERENCE?
Edward H. Schuster, M.D., Alison Freifeld, B.A., and Bernadine H. Bulkley, M.D., F.A.C.C., The Johns Hopkins School of Medicine and Hospital, Baltimore, Maryland.

"Nontransmural" and "transmural" are morphologic terms used clinically to subset patients with myocardial infarction (MI), and controversy exists as to their meaning regarding clinical course. The purpose of this study was to identify true morphologic nontransmural acute (< 21 days old) infarcts at autopsy and compare them to age matched transmural (full-thickness) infarcts, for clinical and pathologic similarities and differences. Comparing 35 nontransmural to 35 transmural infarcts, there was no significant difference with regard to race, sex, chest pain, admission or worst Killip class, arrhythmias, heart block or cause of death; transmural MI's did have a higher frequency of new Q waves (30/35 vs 6/35, $p < .005$). At autopsy, there were no significant differences regarding heart weight, location or numbers of infarcts, severity of coronary disease, age of acute infarct, or size of infarction (18% of left ventricle for nontransmural vs 22% for transmural). Acute thrombi were significantly more common among tansmural MI's (30/35 vs 8/35, $p < .005$). Morphologically the nontransmural infarcts showed mural involvement ranging from 20 to 90% of left ventricle, and histologically showed more reflow (i.e. contraction band) injury (54% of total infarct) compared to transmural infarcts (35% of total) ($p < .05$).

Fatal nontransmural and transmural infarcts have major clinical and pathologic similarities, but differences in type of necrosis and occurrence of coronary thrombi suggest differing pathophysiology. The latter may account for existing differences among clinical studies regarding prognosis.

ANTERIOR TRANSMURAL MYOCARDIAL INFARCTION (AMI). ANALYSIS OF REGIONAL WALL MOTION DURING THE EARLY HOURS WITH AND WITHOUT TOTAL CORONARY OCCLUSION.
Marcus A. DeWood,M.D; J. Paul Shields,M.D, FACC; Gerald R. Hensley,M.D,FACC; Julie Spores,CRNA; Steve Smith,M.D; K.Riggs,M.D; L.Thomas Mouser,M.D,FACC; William P. O'Grady, M.D,FACC, Sacred Heart and Deaconess Medical Centers, Spokane, Washington.

Total coronary occlusion is frequently present during AMI. Although early thrombolysis or release of coronary spasm may occur, little is known concerning the effects of residual blood flow on regional wall motion (RWM) as reflected by regional ejection fraction (EF). We investigated RWM in normal subjects (N=30) and in 50 pts who underwent coronary arteriography and left ventriculography (LV) within 12H of AMI. Group I (N=25) demonstrated total occlusion of the proximal LAD. Group II (N=25) had residual antegrade flow in the LAD. Ventriculograms were divided from the mid aortic valve to the LV apex to obtain a long axis. The anterior wall (AW) of the LV was then divided into 4 equal sections from the apex (area 1) to the base (area 4). Areas 2 & 3 defined the midportion of the AW of the LV. End systolic (ES) and end diastolic (ED) measurements were then made and the difference (ED-ES/ED) expressed as REF in % area change.

*p<0.01	Area 1	Area 2	Area 3	Area 4
Normals	56±10	60±10	63±9	58±6
Group I	16.5±19*	18.1±12*	23.6±11*	36.2±11*
Group II	34.6±15	38.0±14	45.7±14	47.1±9

Thus: 1). RWM is depressed in both groups but residual blood flow is associated with significantly better RWM during the early hours of AMI and 2). Continued myocardial perfusion by patency of the LAD may lead to improved contractile performance.

WEDNESDAY, MARCH 18, 1981
AM
PREVENTION OR REVERSAL OF MYOCARDIAL INJURY
10:30-12:00

INOTROPIC AND CHRONOTROPIC EFFECTS OF INSULIN IN THE CONSCIOUS DOG: CONTRIBUTION OF CATECHOLAMINES AND HYPOGLYCEMIA. Jud U. Doherty, MD; Chang-seng Liang, MD, PhD; Robert T. Faillace, MD; J. Mark Yi, PhD; Stephanie Arnold, BA; Haralambos Gavras, MD; William B. Hood, Jr., MD, FACC, Boston University School of Medicine and Thorndike Memorial Laboratory, Boston, Mass.

Insulin is known to exert an inotropic effect but the mechanism is unclear. To determine whether it is related to catecholamine release or hypoglycemia, we measured heart rate (HR), mean aortic blood pressure (BP), cardiac output (CO), left ventricular dP/dt, and plasma norepinephrine (NE) and epinephrine (E) at control (C), during infusion of 8 milliunits/kg/min of insulin (IN), and during IN plus restoration of plasma glucose (G) to control (IN+G), in 7 conscious, chronically instrumented dogs. Results were:

	HR	BP	dP/dt	CO	G
	bpm	mmHg	mmHg/sec,x10^{-3}	L/min	mg/dl
C	80±5	116±5	2.9±.13	1.68±.19	72±4
IN	96±9*	120±4	4.0±.23*	2.61±.22*	35±2*
IN+G	116±10*	117±2	4.3±.21*	2.98±.21*	72±4

Values are mean±SE; *P<0.05, compared to C.
NE and E increased significantly from 0.36±0.02 and 0.51±0.11 at C to 1.50±0.14 and 3.61±0.60 ng/ml during IN. In a second group (n=7) G was held constant throughout IN; IN increased HR (108±9 to 124±10 bpm), dP/dt (2950±210 to 4090±310 mm Hg/sec), and CO (1.60±0.11 to 2.02±0.20 L/min). In a third group (n=7) with IN+propranolol, BP increased from 121±6 to 140±10 mm Hg with no other changes. In a fourth group (n=7) with IN+propranolol+phentolamine, all hemodynamic changes were abolished. We conclude that IN has a positive inotropic and chronotropic effect which is independent of hypoglycemia and which is mediated by catecholamine release.

REVERSAL OF DIABETIC CARDIOMYOPATHY BY INSULIN TREATMENT Thomas Schaible, PhD; Alwyn Murphy; James Scheuer, MD, FACC, Montefiore Hosp-Albert Einstein Col of Med, Bronx, NY.

Our previous studies have shown isolated hearts from male rats made chronically diabetic (D) with streptozotocin (STZ) demonstrated abnormal contraction and relaxation. To ensure that this response was not due to toxic effects of STZ, rats that were D for 6 weeks were treated with insulin (2-3 units/day) for 15-25 days so that blood glucose was less than 200 mg%. Hearts from treated D animals (TD) were compared with hearts from untreated D animals (UD) (blood glucose > 500 mg%) and non-D control animals (C) in an isolated heart apparatus at left atrial pressures (AP) 5-20 cm H_2O and at fixed heart rates using 5.5 mM glucose as substrate. Means of 6-7 hearts at 15 cm AP were:

	CF[a]	PLVSP	+dP/dt	-dP/dt	MVO2[a]	SW[a]
	ml/min	mm Hg	mm Hg/sec	mm Hg/sec	ml O_2/min	ergs 10^5
UD	109	82	3530	-2370	1.19	1.27
TD	91[1]	99[1]	4710[1]	-2720	1.37	1.53[1]
C	96[2]	94	4260[2]	-2920[2]	1.28	1.40

(CF = coronary flow; SW = stroke work; a = per gram dry LV wt; 1 = $p<.05$, UD vs TD; 2 = $p<.05$, UD vs C)
Increasing AP from 10 to 20 cm resulted in no increase in CO in UD, a 28% increase ($p<.005$) in TD and a 15% increase ($p<.001$) in C. Therefore, the abnormalities in performance of hearts of STZ diabetic rats are reversed by chronic insulin therapy and are not the result of STZ cardiotoxicity. Furthermore, the trend for higher values of PLVSP, +dP/dt and SW in TD compared to C suggests a beneficial effect of chronic insulin therapy on the myocardium.

PROTECTIVE EFFECTS OF VERAPAMIL AND HYDRALAZINE ON THE CARDIOMYOPATHY OF THE SYRIAN HAMSTER Jean-Lucien Rouleau, MD, FRCP(C); Leonard Chuck, PhD; Gabor Hollosi, PhD; Joan Wikman-Coffelt, PhD; Parris Kidd, PhD; William W. Parmley, MD, FACC, University of California, San Francisco, Ca.

Thirty-seven cardiomyopathic (CM) Syrian hamsters, strain UMX7, were injected from day 21 to 90. They were divided into five groups: saline (S), propranolol (P), digoxin (D), verapamil (V) and hydralazine (H). Mechanical studies were performed on their isolated papillary muscles, histologic studies were done on a strip of their left ventricular wall and the rest of the heart was used for actin activated myosin ATPase (AM ATPase) studies. These tests were also performed on 7 normal (C) hamsters.

N	Group	F (g/mm^2)	max/df/dt (g/sec)	Vmax (Lmax/sec)	AM ATPase (μmoles of Pi/mg/min)
7	C	2.5	35	2.7	0.211
9	S	1.6	24	2.0	0.135
7	P	1.6	25	1.9	0.136
7	D	1.2	18	1.5	0.129
7	V	3.0	38	2.8	0.164
7	H	2.2	28	2.4	0.163

Although all the CM groups had lower AM ATPase activities than the control hamsters ($p<0.05$), and none of the drugs could prevent the usual lesions from occurring, verapamil was able to preserve the intrinsic contractility (Vmax, force (F) and df/dt) of the remaining muscle ($p<0.05$). As well, hydralazine helped preserve contractility more than digoxin ($p<0.05$). We found a correlation between the Vmax and the AM ATPase ($R=0.60$), ($p<0.001$). By decreasing intracellular calcium we were able to help preserve the instrinsic contractile state and the AM ATPase activity of the remaining cells.

LIMITATIONS OF HISTOLOGICAL MORPHOMETRIC ANALYSIS IN PREDICTING DRUG PRESERVATION OF CONTRACTILITY IN CARDIOMYOPATHY. Parris Kidd, Ph.D.; Jean-Lucien Rouleau, M.D.; Thomas Yasumura, M.Sc.; Leonard H.S. Chuck, Ph.D.; William W. Parmley, M.D. Univ. of Calif, San Francisco.

Strain UM-X7.1 Syrian hamsters spontaneously develop a lethal cardiomyopathy. To correlate the effects of drugs on muscle damage and contractility, we injected saline, hydralazine, propranolol, digoxin, or verapamil into 30 hamsters from 7 litters twice daily, from days 21 through 90. The papillary muscle was used for mechanical measurements; a strip of LV wall was fixed in glutaraldehyde and embedded in GMA plastic for histology. 4-μm-thick sections cut from 3 levels were stained with Pb hematoxylin and 4 fields of each were examined at 960X under a 100-square counting grid. We measured % active lesions, % healing lesions, % calcifying lesions, and % hypercontracted areas, and from these derived the % undamaged muscle. Litter-to-litter variability limited statistical analysis, but definite trends were evident. None of the drugs prevented muscle damage completely. Partial prevention of muscle damage did not correlate with preservation of contractility (Rouleau et al., these proceedings). Verapamil, which partially prevented muscle damage (mean +SD, 88.9±4.2% vs 77.2±10.8% for controls, $P<0.1$) preserved contractility well (Vmax 2.8±0.5 vs. 2.0±0.5 for controls), but propranolol, which also prevented muscle damage (90.4±4.1%, $P<0.1$), preserved contractility poorly (Vmax 1.9±0.5); hydralazine, which partially preserved contractility, did not prevent muscle damage. However, the frequency of hypercontracted areas correlated inversely with the preservation of contractility by each drug (for developed force, $R=0.29$, $P<0.1$; for V max, $R=0.35$, $P<0.05$). Verapamil, which preserved contractility best, reduced hypercontracted areas strikingly (0.1±1.3% vs. 5.0±4.9% for controls).

TIME COURSE OF VULNERABILITY TO REPERFUSION-INDUCED VENTRICULAR FIBRILLATION. David A. Cox, Richard Verrier, Ph.D., F.A.C.C., Kenneth Baughman, M.D., Bernard Lown, M.D., F.A.C.C. and Stephen F. Vatner, M.D. From the Depts. of Med., Harvard Med. Sch., Peter Bent Brig. Hosp. and Harvard Sch. of Pub. Health, Boston, MA 02115

It has been well documented that acute coronary artery (CA) reperfusion following CA occlusion (O) is associated with reduced threshold to ventricular fibrillation (VF) and consequently, a high incidence of VF. It is not known how long after CAO that reperfusion will elicit increased susceptibility to VF, although reports have indicated this occurs with CA reperfusion 1 hr after CAO. In contrast, we have observed in 14 consecutive conscious dogs no instances of VF upon release of CAO after 1 hr. To examine the time course of susceptibility to VF, 15 additional dogs were instrumented with an hydraulic occluder and a single crystal CA Doppler flow probe to confirm CAO and reperfusion. One wk later, using chloralose anesthesia, VF thresholds were determined with a single 10 msec stimulus delivered through a transvenous bipolar catheter positioned in the apex of the right ventricle.

	VF THRESHOLD (MILLIAMPERES)		
	Pre-CAO	CAO	REPERFUSION
10' CAO (n=5)	22 ± 3 (Mean ± SE)	12 ± 2*	8 ± 2*
30' CAO (n=5)	23 ± 3	14 ± 3*	10 ± 3*
45' CAO (n=5)	21 ± 2	12 ± 1*	25 ± 4

* significantly different from pre-CAO, $p<0.05$.

Thus, as has been shown previously, VF threshold falls with CAO and falls further with release of CAO at 10 min. However, in contrast to what has been suspected, this phenomenon changes radically between CAO of 30 and 45 min. Interestingly, this reduction in susceptibility to VF is nearly coincident with the time course of irreversibility of cell death, which could be of importance in understanding the mechanism of this lethal arrhythmia.

DOES NIFEDIPINE PROTECT AGAINST REPERFUSION DAMAGE? Pieter D. Verdouw, Ph.D., Folkert J. ten Cate, MD, Hans M. Hartog, BS, Paul G. Hugenholtz, MD, FACC, The Thoraxcenter, Erasmus University, Rotterdam, The Netherlands.

Sudden reperfusion (R) of ischemic myocardium (Isch) may cause further disturbances in calcium metabolism, (so called) reperfusion arrhythmias and myocardial damage. Since Nifedipine (N) is a calcium antagonist, its efficacy during R was tested in 24 pigs in whom the left anterior coronary artery (LAD) flow was reduced to 22%. Before reduction (red) systolic wall thickening (swt) was 42 ± 3% of the end-diastolic thickness (edt). After red there was no systolic thickening. All animals were reperfused after 30 minutes of low flow. Eight animals served as controls (C), 8 received an infusion of 2 $\mu g/kg^{-1}$ (L) and 8 an infusion of 15 $\mu g/kg^{-1}$ of N (H), from 10 min. prior to R until 5 min. of R. During red, the overall hemodynamic effects of H were slight, but systemic vascular resistance declined by 20% and left ventricular end-diastolic pressure by 16%. With H regional myocardial flow, measured by microspheres, to the ischemic zone increased from 22 to 36% ($p<0.05$) without an improvement in swt. Flow to the control zone increased by 20% ± 6% ($p<0.05$) without change in swt. During subsequent R, swt recovered to only 20 ± 2% of edt for L and C, but increased to 35 ± 3% (80% of C value) for H ($p<0.05$). Moreover during R, severe ventricular ectopics were observed in all C, but in only 1 H. We conclude that timely administration of N before and during R will prevent severe ventricular rhythm disturbances and enhance recovery of regional myocardial function.

WEDNESDAY, MARCH 18, 1981
AM
ECHOCARDIOGRAPHY: VENTRICULAR FUNCTION II
10:30-12:00

QUANTITATIVE DOPPLER FLOW ESTIMATORS: IMPROVED CHARACTERIZATION AND SEPARATION OF NORMAL FROM ABNORMAL FLOW. Larry Miller, PhD; William J. Bommer, MD, FACC; Dean T. Mason, MD, FACC; Anthony DeMaria, MD, FACC; University of California, Davis, California.

The detection of abnormally disturbed flow in previous pulse Doppler studies has been limited by M-mode imaging, noisy receivers, gain dependent output displays, and high velocity aliasing. Thus, we built a high-gain low-noise Doppler detector and a hi-fidelity microprocessor-based spectral analyzer (fast Fourier transform) and added it to a 2D-echo Doppler instrument for accurate positioning of the sample volume. This system features improved signal-to-noise ratios (20db better than commercial units); the ability to avoid high-velocity aliasing with unidirectional flow; and gain independent spectral displays with high velocity resolution (43 Hz), high time resolution (12ms), and a 32-level grey scale. Using the median absolute deviation (MAD) of the Doppler frequency as a measure of the velocity distribution spread in blood, we evaluated blood flow patterns in 10 normal subjects. The Doppler MAD in normals ranged from 400-860 Hz aorta, 220-770 Hz right atrium, 130-690 Hz right ventricle, 180-860 Hz pulmonary artery, 270-900 Hz left atrium and 130-860 Hz left ventricle. These flow patterns and MAD's differed significantly from the abnormal flow patterns and MAD's (900-2000 Hz) ($p<.01$) seen in 30 patients with mitral stenosis (5), aortic stenosis (8), mitral regurgitation (10) and aortic regurgitation (10). Thus, improved Doppler systems can eliminate many of the prior limitations of the technique and yield detailed hard copy print outs of cardiac flow patterns. The analysis of these flow patterns yields quantitative statistical parameters which can be used to objectively distinguish normal flow from abnormally disturbed flow.

ROLE OF TWO-DIMENSIONAL ECHOCARDIOGRAPHY IN EVALUATION OF PATIENTS WITH POST MYOCARDIAL INFARCTION VENTRICULAR SEPTAL DEFECT
Harry L. Bishop, MD; Robert S. Gibson, MD; George A. Beller, MD, FACC; Randolph P. Martin, MD, University of Virginia, Charlottesville, Va.

In patients (pts) with suspected ventricular septal defect (VSD) following MI, bedside hemodynamics may not permit the definitive diagnosis and cannot assess LV wall motion. Two-dimensional echocardiography (2DE) may allow the noninvasive diagnosis and localization of a post-MI VSD and provide an assessment of overall LV function. In 7 pts with a recent MI, VSDs were detected by 2DE and localized to the inferior septum in 3 and anterior septum in 4. All VSDs were confirmed by catheterization, surgery, and/or post-mortem exam. The subcostal and apical 4-chamber views with anterior and posterior transducer angulation were the optimal views. A septal aneurysm was detected in all pts. In 5 of 5 pts, a negative contrast effect was seen in the RV after the IV injection of saline. To assess global and segmental LV function, a LV wall motion index (WMI) was calculated using an 11 segment analysis (-1 hyperkinetic, 0 normal, +1 hypokinetic, +2 akinetic, +3 dyskinetic; WMI=total score/number of segments analyzed). Of 77 possible segments, 75 were interpretable. The WMI in the 4 survivors (mean 0.77 ± .41) was lower than in the 3 nonsurvivors (mean 1.66 ± .24; $p<.021$). There was no difference in the mean age, peak creatine kinase, VSD location, or Killip class. Monitoring of LV function by 2DE aided in guiding the timing of angiography and surgery in 5 pts. In the remaining 2 pts the detection of marked LV dysfunction by 2DE was instrumental in the decision for no further invasive studies or surgery. 2DE permits the noninvasive diagnosis and localization of post-MI VSD, provides prognostic information, and aids in management decisions.

THE EFFECT OF ALCOHOL ON LEFT VENTRICULAR RELAXATION IN CORONARY ARTERY DISEASE: ECHOCARDIOGRAPHIC ASSESSMENT BY COMPUTER ASSISTED ANALYSIS OF LEFT VENTRICULAR WALL VELOCITY.

John S. Gottdiener, MD; Lucy Van Voorhees, MD; Judy Gay; Robert DiBianco, MD,FACC; Dan L. Maloney, MSEE; Ross D. Fletcher, MD,FACC. Veterans Administration & Georgetown University Medical Centers, Washington, D.C.

Although ethyl alcohol may have adverse effects on systolic left ventricular (LV) function, its effects on diastolic LV function in patients with coronary artery disease (CAD) are uncertain. In order to determine the effects of alcohol on diastolic LV function, echocardiograms (echo) were done in 12 pts with CAD before and after 180 ml of 40% alcohol given p.o. over a 1 hour period. The septal endocardial surfaces and endo and epicardial surfaces of the LV posterior wall were digitized at 3 msec intervals in 7 pts with high-quality echos using a tablet digitizer and dedicated microcomputer. After alcohol (av plasma level 99±4 SEM mg%) the av peak LV diastolic filling rate, normalized by the instantaneous LV internal dimension, decreased from 3.0±0.5 sec^{-1} to 1.8±0.1 sec^{-1} ($p<0.03$). Decreases which were not statistically significant occurred in av normalized peak rates of diastolic thinning of the septum (before alcohol 2.7±0.4 sec^{-1}, after alcohol 2.5±0.3 sec^{-1}) and LV posterior wall (before alcohol 4.5±0.8 sec^{-1}, after alcohol 3.5±1.3 sec^{-1}). Parameters of systolic function, i.e. fractional shortening, mean Vcf, normalized peak rates of septal and posterior wall thickening, and peak Vcf were unchanged by alcohol.

Hence, alcohol may impair LV diastolic filling even without depression of LV systolic function. Alcohol should be used with caution in CAD pts prone to pulmonary congestion.

DIFFERENTIATION OF CONSTRICTIVE PERICARDITIS AND RESTRICTIVE CARDIOMYOPATHY BY ECHOCARDIOGRAPHY

Richard A. Meyer, M.D., FACC, Gregory G. Janos, M.D., A. Kalavathy, Peter Engle, M.D., Samuel Kaplan, M.D., FACC, Children's Hospital Medical Center, Cincinnati, Ohio.

Constrictive pericarditis (CP) and restrictive cardiomyopathy (RC) may be indistinguishable clinically and hemodynamically. Computer analysis of digitized M-mode echo was used to study left ventricular (LV) diastolic function in four patients with CP, three with RC and 40 normal controls (C). The echoes were digitized by an on-line mini computer and measurements were taken from the printouts of the plotted contour of the LV chamber and posterior wall (LVPW). Values found normally to be related to heart rate were corrected by regression equation and presented as % of normal. The results are as follows:

	Normalized Rates (mean± SD sec^{-1})		Intervals (mean± SD)		
PT	Max. Filling LV	Max. Thin LVPW	Major Filling LV+	Total Thin LVPW+	Min. Dim. to Max. Fill LV (sec)
C	3.2 ± 0.8	-6.3 ± 1.5	-	-	0.08 ± 0.02
RC	2.3 ± 1.0*	-2.3 ± 1.1*	129 ± 4	142 ± 29*	0.11± 0.03*
CP	3.9 ± 1.2♣	-3.9 ± 1.6*♣	79 ± 9♣	163 ± 18*	0.05± 0.01*♣

* = versus control, ♣ = versus RC at $p < .05$; + = % normal

Diastolic function of the LV is abnormal in both RC and CP; however, the rate and duration of filling as well as LVPW pattern of relaxation are charcteristic for each group and appears to permit separation of RC from CP. Therefore, digitized echo may prove useful in differentiating these two conditions which frequently produce diagnostic dilemmas because they have similar clinical and hemodynamic features.

DIAGNOSIS OF PACING CATHETER PERFORATION BY REAL TIME TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Bapineedu Gondi, MD, Navin C. Nanda, MD, FACC, University of Rochester Medical Center, Rochester, NY

Myocardial wall perforation produced by RV temporary transvenous pacing catheters (PCs) was identified in 5 patients (pts) by real time two-dimensional echocardiography (ATL 90° scanner). In 3 pts with loss of sensing and/or increased pacing threshold, the PCs which presented as dense, linear echoes with posterior reverberations could be seen passing through the RV apex with the tip located 2mm - 1cm outside the cardiac border. Perforation was not suspected on chest X-rays or 12-lead pacing ECGs. Pericardial effusion developed in 2 of 3 pts (1 localized, 1 generalized) but did not increase in size and was not associated with cardiac tamponade. In 1 pt PC was repositioned under echo control in another area of the RV apex with marked decrease in pacing threshold. In the 4th pt, the catheter was seen to extend through the atrioventricular septum into the LV and the tip was in contact with the posterior wall. In the 5th pt the catheter had partially penetrated the ventricular septum near the apex without entering the LV cavity. Both these pts showed right bundle branch block patterns on the pacing ECGs and chest X-rays showed PC malposition without pinpointing the exact location. In 4 of 5 pts the identification and abnormal location of the PC was confirmed during PC withdrawal when the movements of the PC could be seen to correspond with manual manipulations. Withdrawal intracardiac electrograms were done in the 5th pt and in 1 pt with RV apical perforation and showed changes typical of perforation. Autopsy verification of perforation was available in 2 pts including 1 pt in whom the RV apical PC was not withdrawn. In conclusion, two-dimensional echocardiography is a useful, non-invasive, non-ionizing tool which provides direct evidence for PC perforation.

SUPERIORITY OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY CRITERIA FOR MEASURING WALL THICKNESS BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Michael J. Barrett, MD; Larry Jacobs; Jonathan Gomberg; Lynn Horton; Robert Leyrer; Theodore Krouse, MD; Steven G. Meister, MD,FACC, Medical College of Pennsylvania, Philadelphia, Penna.

Three conventions have been proposed for measuring wall thickness (WT) of the left ventricle by echocardiography: Convention 1 = leading edge to trailing edge (traditional), convention 2 = trailing edge to leading edge (Penn), and convention 3 = leading edge to leading edge (American) Society of Echocardiography)(ASE). No direct comparison of these conventions with anatomic WT and cavity area (A) has been performed using 2-dimensional echo (2D Echo). Therefore, we tested each convention in 11 phantom heart tomograms, using a phased array system. Circular phantoms were constructed from 1cm strips of fresh, unfixed sharply-cut bovine muscle. Anatomic WT and A were measured directly with an XY plotter. Phantoms were then immersed in a water bath and 2D Echo images recorded. Eighty wall segments were measured by each convention:

Method	M±sem	% error	t-test
Anatomic WT	11.0mm±.02	-----	-----
Convention 1	16.0mm±.02	46%±1.0	p<.001
Convention 2	8.4mm±.02	24%±2.0	p<.001
Convention 3	12.0mm±.02	16%±1.2	p=ns

Results of cavity area were similar. Convention 1 underestimated A by 25%±3.6 (p<.001). Convention 2 overestimated A by 19%±3.1, p<.01) and convention 3 underestimated A by 12%±2.5 (p=ns).

Conclusion: The leading edge to leading edge convention recommended by ASE is more accurate than other conventions for measuring wall thickness and cavity area by 2D echo when compared to anatomic measurements.

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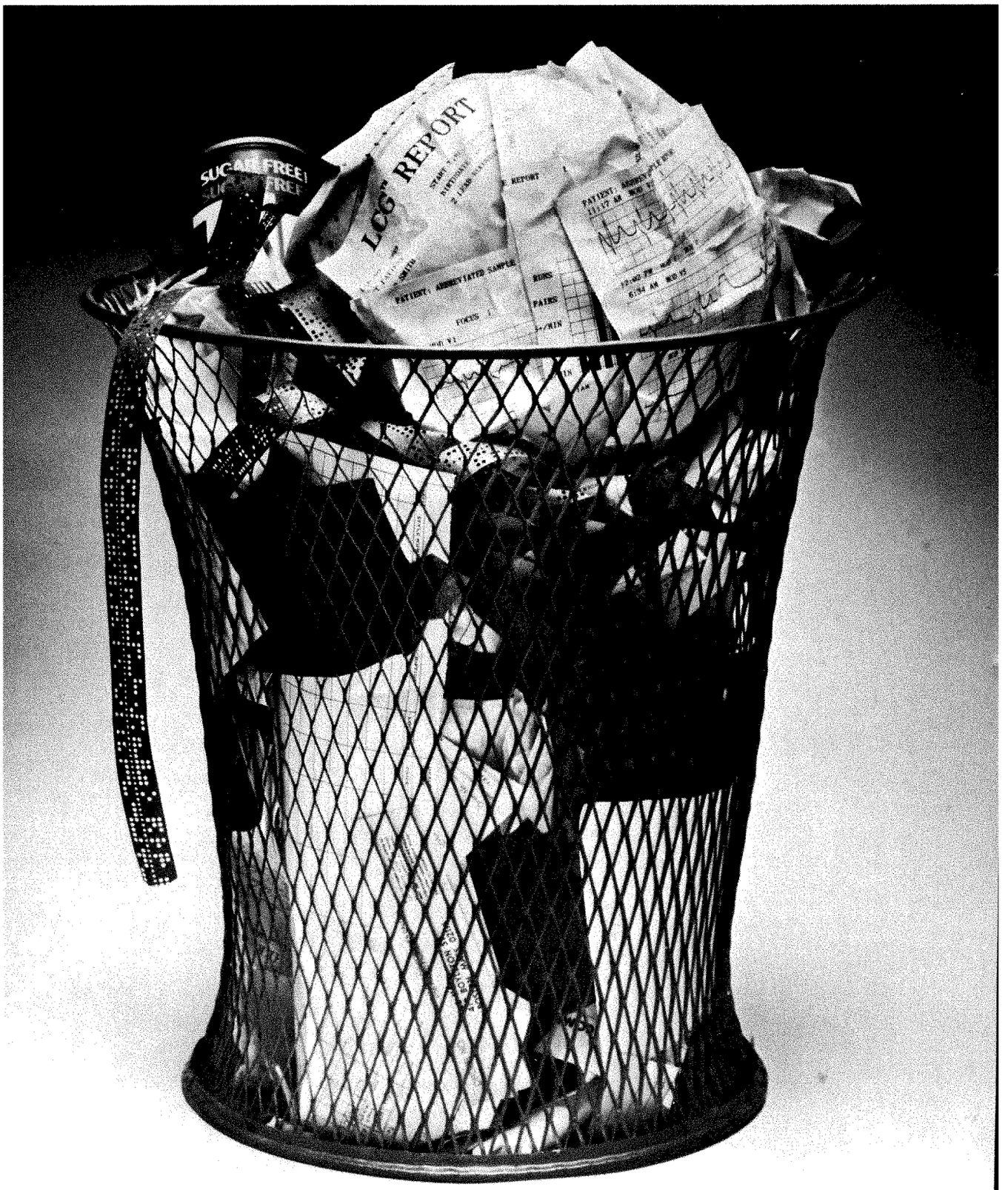

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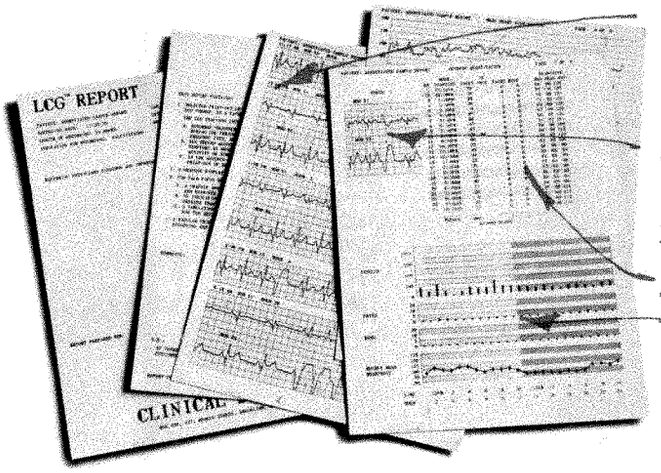

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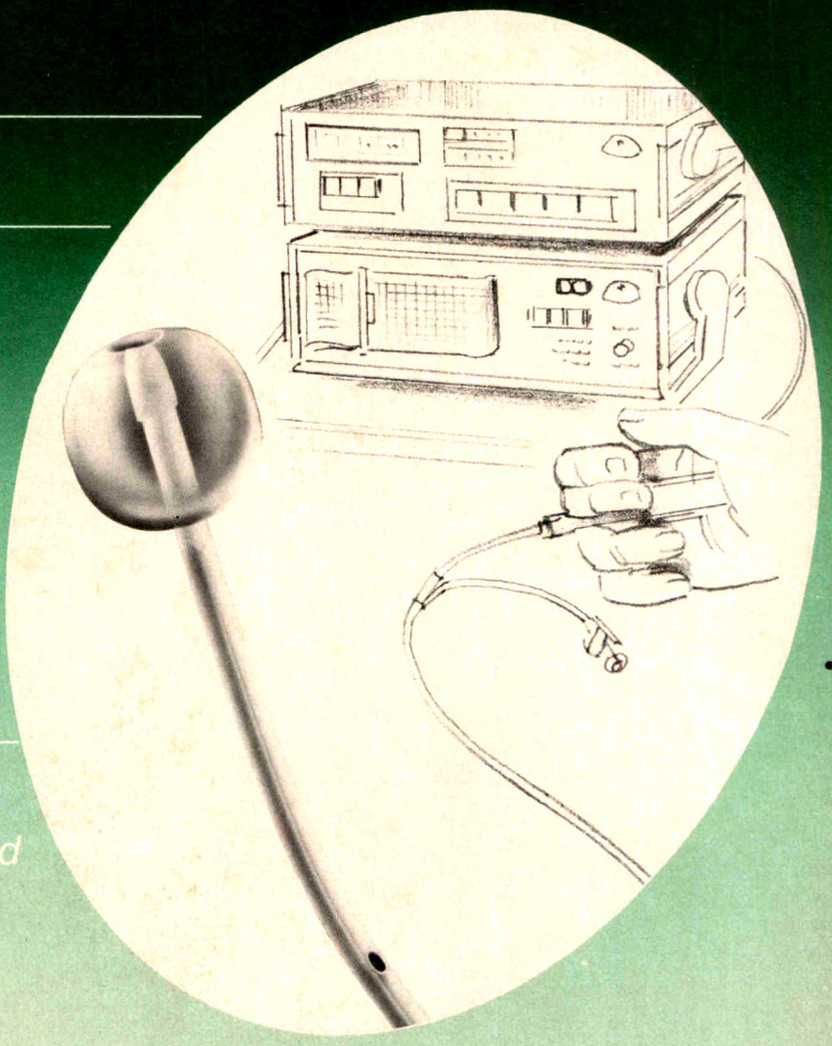

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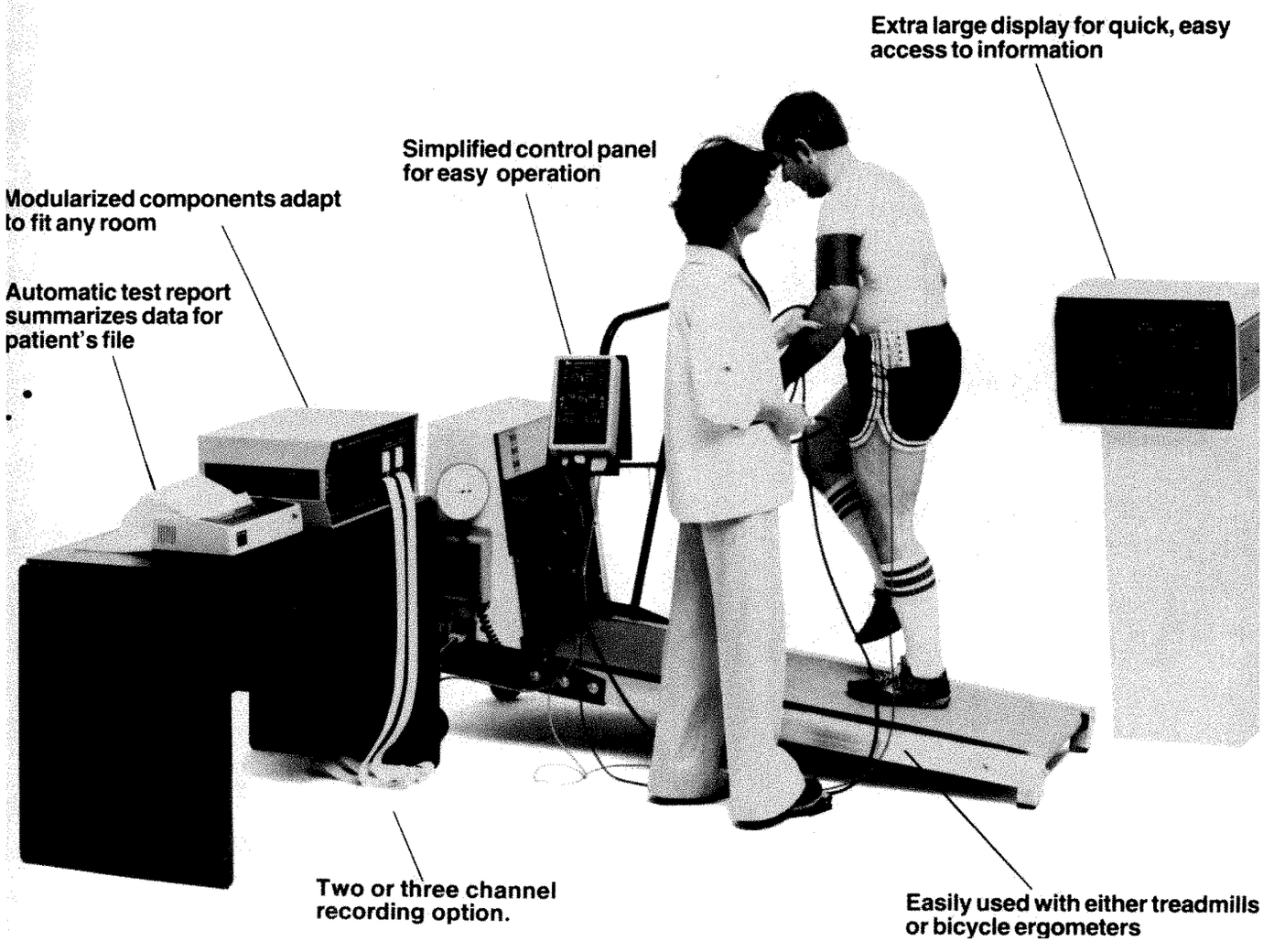

WEDNESDAY, MARCH 18, 1981
AM
CORONARY ARTERY DISEASE: MEDICAL THERAPY
10:30-12:00

EXACERBATION OF ISCHEMIA IN VASOTONIC ANGINA PECTORIS BY PROPRANOLOL. Rose M. Robertson, MD, FACC; Alastair J.J. Wood, MD; Yvonne Bernard, RN; David Robertson, MD, Vanderbilt University Medical Center, Nashville, TN.

Propranolol (P) has been reported to improve vasotonic angina (VA), a syndrome characterized by chronic recurrent episodes of ischemia due to coronary artery spasm. We performed 7 double-blind, placebo(PLA)-controlled trials of P in 6 patients (pts) with VA (ages 51-72, 3 male, 3 female). Coronary anatomy ranged from normal to 70% stenosed. Continuous ECG monitoring was used to document ischemic episodes. Both low-dose (LD) P (40 mg po q6h) and high-dose (HD) P (160 mg po q6h) were used. Serum levels were obtained in four pts (mean=52, range 28-74 ng/ml on LD-P; mean=280, range 222-342 ng/ml on HD-P). Ischemic episodes on PLA were compared to those on P and to those during a PLA period after P washout.

	MEAN LENGTH OF EPISODES(min)				TOTAL TIME ISCHEMIC/DAY(min)			
Trial	PLA	LD-P	HD-P	PLA	PLA	LD-P	HD-P	PLA
1	0.0	4.1	9.1	0.0	0.0	4.1	9.1	0.0
2	2.4	3.9	6.1	0.0	2.4	23.4	48.8	0.0
3	1.9	-	4.5	1.1	34.2	-	76.2	13.9
4	0.6	0.5	0.7	0.5	16.6	19.5	21.0	12.0
5	2.0	4.8	5.2	1.3	18.7	38.4	91.7	8.3
6	1.3	3.4	3.7	1.9	13.4	27.2	25.9	15.8
7	5.4	6.5	6.2	4.5	178.2	116.8	155.0	115.0
mean	1.3	3.1*	3.4*	1.3	37.6	38.2	61.1*	23.6

* = $p<0.05$

With P all pts increased either the length or frequency of ischemic episodes, or both. Four of 5 additional VA pts had an increase in angina on P by history. Thus, P was detrimental in 9 of 11 pts with VA, unrelated to underlying coronary anatomy. No patient was significantly improved. Propranolol should be avoided in patients with chronic recurrent coronary artery spasm.

DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED COMPARISON OF PROPRANOLOL AND VERAPAMIL IN PATIENTS WITH STABLE, EXERTIONAL ANGINA PECTORIS. SM Johnson, MD, DR Mauritson, MD, J Corbett, MD, JT Willerson, MD, FACC, LD Hillis, MD, FACC, U of Texas Health Science Center, Dallas, TX.

This study was performed to compare the relative efficacies of propranolol (P) and verapamil (V) in patients with stable, exertional angina (A). In 18 patients (16 men, 2 women, mean age 58 yrs) with coronary artery disease and A, low (40mgq6h) and high (80mgq6h) doses of P were compared to low (80mgq6h) and high (120mgq6h) doses of V in a double-blind, randomized, placebo(Pl)-controlled study lasting 7½ weeks (wks): 2 wks Pl "run-in," 2 wks P or V (1 wk low dose, 1 wk high dose), 1½ wks Pl "wash-out," and 2 wks P or V (1 wk low dose, 1 wk high dose). During each period the following were quantitated: (1)chest pains/wk, (2)nitroglycerin (NTG) used/wk, (3) transient ischemic ST segment deviations (STD) on 2 channel Holter monitoring, and (4)response to supine bicycle exercise, including ECG analyses and an assessment of LV volumes and ejection fraction (EF) by equilibrium gated blood pool scintigraphy. The 2 Pl periods were similar.

	A/wk	NTG/wk	STD/day	Rest-EF	Exercise-EF
Pl	6.6±9.7	10.0±15.4	2.2±2.9	57±16	53±18
Hi-P	3.1±7.6*	5.4±13.7	1.2±1.9	60±16	57±16*
Hi-V	1.7±2.7*	2.4±3.9*	0.6±1.2*	54±14	50±14

(All figures are mean±SD; * $p<0.05$ when compared to Pl.)

Hi-P and Hi-V were similarly efficacious in the relief of A. NTG use and the incidence of STD were lowest with Hi-V. LVEF during rest and exercise was slightly higher during Hi-P than during Hi-V. Thus, in a double-blind, randomized study of patients with stable angina, (1)propranolol and verapamil are of similar efficacy in the relief of angina, and (2)neither agent induces important LV depression. Verapamil is a suitable and effective alternative to propranolol in the patient with stable angina.

ORAL VERAPAMIL VS PROPRANOLOL IN CORONARY ARTERY DISEASE: EVALUATION OF LEFT VENTRICULAR FUNCTION BY EXERCISE RADIONUCLIDE VENTRICULOGRAPHY. Martin A. Josephson MD, Harvey S. Hecht MD, FACC, James M. Hopkins BS, and Bramah N. Singh MD, PhD, FACC. Wadsworth VA Medical Center and University of California, Los Angeles, California.

Although the antianginal actions of verapamil (V) are known, the effects of chronic V therapy on exercise left ventricular ejection fraction and exercise induced regional wall motion abnormalities (RWMA) in patients (pts) with coronary artery disease (CAD) and its effects compared to propranolol (P) are unclear. Therefore, 18 pts with CAD underwent supine multistage bicycle exercise during placebo control (C), V 120 mg and P 80 mg qid treatment according to a randomized single blind crossover design. EF and exercise induced RWMA were determined by equilibrium radionuclide blood pool imaging. 4 of 18 pts had a normal exercise response, i.e. > .05 increase in EF and no exercise induced RWMA. 14 pts had an abnormal exercise response and EF, RWMA, heart rate (HR), and systolic blood pressure (BP) at the same maximal workload are shown for this group of pts. Results are shown as mean ± standard deviation.

		EF	RWMA	HR	BP
REST	C	.53±.11		67±13	130±15
MAXIMUM EXERCISE	C	.46±.11	17	124±18	165±21
	V	.50±.12*	7*	113±16**	160±21
	P	.50±.12*	12	91±10**	143±14**

(*$p<.05$, **$p<.01$ compared to control exercise)

Conclusions: 1) Both V and P decrease the extent of exercise induced reduction in EF in CAD pts. 2) V decreases the number of exercise induced RWMA, 3) maximal exercise HR is decreased by both V and P; only P reduces BP at maximal exercise.

PROGNOSIS OF VARIANT ANGINA PATIENTS TREATED WITH CALCIUM ANTAGONIST DRUGS

David D. Waters, MD, FACC; Jadwiga Szlachcic, MD; Pierre Théroux, MD, FACC, Montreal Heart Institute, Montreal, Que

Following hospital discharge 100 consecutive variant angina (VA) pts were followed for 17.6 (range 1-60) months. Each had exhibited rest angina with transient ST elevation relieved by nitroglycerin. Mean age was 51.4 (range 26-70) years; 67 were men. ST elevation was anterior in 52, inferior in 46 and both simultaneously in 2. One, 2 and 3 vessel disease were present in 40, 12 and 2 pts; 44 had no stenosis >70%; 2 did not undergo arteriography.

Perhexiline was the only calcium antagonist available to treat the first 25 pts; 16 became asymptomatic, 3 had only effort angina, VA persisted in 4 and 2 developed MI. Of 24 pts treated with nifedipine 21 were asymptomatic, 1 had effort angina and VA persisted in 2. Of 12 treated with diltiazem, 11 were asymptomatic and VA continued in 1. Of 14 treated with verapamil, 13 were angina-free and 1 had VA. Thirteen pts were discharged on both nifedipine and diltiazem: 7 were asymptomatic, 1 had effort angina and 5 had VA. Of 9 pts treated with oral nitrates alone, 5 were asymptomatic, 1 had effort angina and 3 developed MI. Bypass surgery was initial treatment in 3 and was done later in 6 others. Calcium antagonists were discontinued in 28 asymptomatic pts. VA recurred in only 4 but within 2 weeks 2 others developed MI. Overall 4 pts died, all within 12 months, 1 with MI, 1 by suicide and 2 suddenly, 1 with normal arteries taking perhexiline and 1 off drug after bypass surgery. MI occurred in 7 others, within 3 months in 6. Two of these 7 had no stenosis >50%. MI or cardiac death did not occur in any pt while taking nifedipine, diltiazem or verapamil.

We conclude that prognosis in VA improves after the initial phase of the disease. MI and death are not limited to pts with fixed lesions. Nifedipine, diltiazem and verapamil appear to be equally effective treatment.

BENEFICIAL EFFECTS OF DILTIAZEM ON EXERCISE PERFORMANCE IN PATIENTS WITH CORONARY ARTERY DISEASE AND ANGINA PECTORIS

Mark R. Starling, MD; Michael H. Crawford, MD, FACC; Robert A. O'Rourke, MD, FACC, University of Texas Health Science Center and Veterans Administration Hospital, San Antonio, Texas.

Diltiazem, a new slow-channel Ca++ blocking agent, has potential value in the treatment of patients (pts) with angina pectoris principally because of its vasodilator action on coronary and systemic arteries. Accordingly, we studied 10 pts with fixed coronary artery disease who had reproducible chest pain and $\geq$1 mm of ST-segment depression (ST↓) on treadmill exercise testing performed before and after one week control period of single-blind placebo administration. Subsequently, over a six week period, diltiazem (30 mg) or placebo was administered during sequential weeks in a randomized double-blind crossover fashion as one tablet QID, two tablets TID and two tablets QID for a total diltiazem dose of 120, 180 and 240 mg/day, respectively. Treadmill exercise was performed at the end of each week. Diltiazem at 120 and 180 mg/day did not alter exercise performance as compared to placebo. However, diltiazem 240 mg/day significantly increased time to angina by 1.9 min ($p<.05$), time to ST↓ by 2.2 min ($p = .01$), time to maximal exercise by 2.4 min ($p<.02$), and heart rate at maximal exercise by 14 beats/min ($p<.05$) without effecting the maximal heart rate-systolic blood pressure product compared to placebo values. In addition, two pts no longer had angina and two different pts did not develop ST↓ during treadmill exercise testing at the 240 mg/day dose. During the entire study, no adverse reactions were reported. We conclude that 240 mg of diltiazem a day significantly improves exercise performance in pts with angina pectoris due to fixed coronary artery disease and adverse side effects, rarely, if ever, occur at this dosage.

THE THERAPEUTIC AND ECONOMIC IMPACT OF NORMAL CORONARY ARTERIOGRAMS IN PATIENTS WITH SEVERE CHEST PAIN

David P. Faxon, MD, FACC; Doreen E. Kriegel, BS; Carolyn H. McCabe, BS; Thomas J. Ryan, MD, FACC, Boston University Medical Center, Boston, MA

A significant number of patients (pts) with severe angina (A) or intractable atypical pain (AP) referred for coronary arteriography (CA) are found to have normal vessels (NV). To determine what therapeutic or economic benefit may be derived from these studies we analyzed the data of 72 consecutive pts with NV (42 males, 30 females) followed for two years. The initial diagnosis was A in 46 and AP in 26. The mean age for A pts (45 years) differed from AP pts (49 years, $p<0.05$). Comparing the two year period prior to and following CA, the average number of hospital days/pt declined from 14.6 to 3.9 days ($p<0.005$) while the average number of hospital admissions/pt declined from 1.4 to 0.4 ($p<0.005$). This resulted in a decrease in estimated hospital costs/pt from $7300 to $1950 ($p<0.005$). Following CA, 33 of 42 (79%) A pts were reclassified as AP by their physicians ($p<0.001$). The number of pts taking Inderal before vs. after CA was reduced significantly (47/72 vs 26/72, $p<0.05$). Likewise the number of pts taking nitrates fell (57/72 vs 30/72, $p<0.05$). Employment status was not effected in this analysis. Results from a patient questionnaire indicated improvement in functional status following CA in 66% of pts.

We conclude, in pts referred for CA with severe chest pain complaints, the documentation of NV by CA not only alters the clinical assessment of symptoms; improves functional status and modifies medical therapy but also reduces hospitalization and subsequent medical cost. These therapeutic and economic benefits deserve consideration in any evaluation of CA for its overall effectiveness.

WEDNESDAY, MARCH 18, 1981
PM
ELECTROCARDIOGRAPHY
2:00-3:00

Q WAVES AND TRANSMURAL INFARCTS: THE TERMS ARE NOT THE SAME

RE Ideker, GS Wagner, KA Reimer, DR Alonso, SP Bishop, CM Bloor, JT Fallon, GJ Gottlieb, DB Hackel, HR Phillips, SF Roark, WJ Rogers, WK Ruth, RM Savage, RH Selvester, RM Ward, Duke Hosp., Durham, NC, U. Ala. Med. Ctr., Birmingham, Ala., UCSD Sch. of Med., LaJolla, CA, Mass. Gen. Hosp., Boston, MA, Cornell Med. Ctr., New York, NY, Rancho Los Amigos Hosp., Downey, CA.

The term transmural myocardial infarct (MI) is frequently used as a synonym for significant Q waves in the electrocardiogram (ECG). The purpose of this study was to determine if these two terms are equivalent. The presence or absence of significant Q waves in transmural and non-transmural MI's was studied by quantitative postmortem analysis of human hearts with a single MI. Patients were excluded if the ECG showed left or right ventricular hypertrophy, bundle branch block, or fascicular block. Each of 66 hearts was cut into 5-7 slices and the percent of the left ventricle (LV) infarcted was determined by computer-assisted planimetry. An MI was called transmural if it extended to the epicardium for at least 1 cm in any slice. Significant Q waves were defined as Q waves $\geq$30 ms in any of these leads: I, II, aVL, aVF, or V_1-V_6; an R wave $\geq$40 ms in V_1, or an R wave $\geq$ 50 ms in V_2. Mean size of 37 transmural MI's (23% of the LV $\pm$ 12% S.D.) was greater ($P<0.001$) than that of 29 non-transmural MI's (7%$\pm$5%). ECG's of all cases of transmural MI's and 20 cases (69%) of non-transmural MI's had significant Q waves. Mean MI size for the 20 non-transmural cases with significant Q waves (9%$\pm$6%) was larger ($P<0.001$) than that for the 9 non-transmural MI's without significant Q waves (3%$\pm$2%). Thus the terms Q wave and transmural MI are not synonymous, rather a significant Q wave indicates a large or medium sized MI, whether or not it is transmural. A single MI without associated Q waves is small.

DOES MYOCARDIAL SCAR SIZE PREDICT THE ELECTROCARDIOGRAPHIC FRONTAL PLANE AXIS?

Christopher J. Havelda, MD; R. Chris Hand; Nancy C. Flowers, MD, FACC; Leo G. Horan, MD, FACC; University of Louisville, Louisville, Kentucky.

In order to demonstrate the influence of myocardial scar size on the observed frontal plane axis of the electrocardiogram, serial dissections were undertaken in 1410 human hearts in which correlative electrocardiograms were available within 90 days of death. A strict protocol was employed requiring independent weighing of right and left ventricles and quantitation of myocardial scar size in each of 15 left ventricular zones. A predicted frontal plane axis was derived from a computational model in each of 422 specimens bearing myocardial scars. This model comprised 15 left ventricular and 4 right ventricular segments with vectors perpendicular to the activation wave front of each segment. The vector in each left ventricular segment was reduced proportionate to the amount of myocardial scarring in that segment and a predicted frontal plane axis for each specimen was derived by summation of these 19 resultant vectors. Multivariate analysis comparing the observed frontal plane axis with left ventricular weight, right ventricular weight, and age, demonstrated poor correlation ($r=0.283$). Bivariate analysis comparing the observed frontal plane axis with the predicted frontal plane axis demonstrated good correlation overall ($r=0.695$). When hearts with small scars (no zone invaded by > 33%) were excluded, the correlation rose to 0.739 ($n=216$). The 99% confidence limits for this correlation are 0.647 to 0.808. Hence, in the presence of myocardial scarring, the quantitative loss of vectorial forces primarily determines the resultant observed frontal plane axis.

DETERMINATION OF CARDIAC DIPOLE LOCATIONS DURING VENTRICULAR RECOVERY IN NORMAL MEN. David M. Mirvis and Mark A. Holbrook, University of Tennessee, Memphis, TN.

Dipole ranging is a method to quantitatively determine the location, moment and sense of the heart vector or dipole from body surface measurements. This technique was applied to ECG data recorded from 150 torso electrodes on 45 normal men. Signals were processed to yield isopotential maps and to compute the 6 terms (X,Y,Z locations and X,Y,Z moments) of the dipole best fitting the recorded potentials at 2 msec intervals during QRST. Dipole terms were calculated by solving the Gabor-Nelson surface integration formulae. During QRS, the dipole locations were often extrathoracic; this correlated with isopotential patterns that were overtly nondipolar. In contrast, all maps during STT were dipolar in form. The cardiac dipole remained relatively stationary during STT. Forty msec into STT, the mean location was 1.29" to the left and 1.02" anterior to the center of chest at a level 5.54" below the sternoclavicular joint. Mean location moved only 0.53" throughout the STT. The standard deviation of distance from each location to the mean site was 0.70". Thus, dipole locations were closely grouped near the cluster center, which approximated a point near the left ventricular free wall. Dipole moments rose progressively to a peak during T (0.53± 0.20 mA-cm). Orientation remained inferior, leftward and anterior during STT, with less than a 10 degree shift. Thus, the dipole during most of repolarization may be modeled as a fixed location, fixed orientation, variable strength electrical source. Dipole ranging can therefore provide physiologically relevant information when applied to clinical electrocardiographic problems; localization of the cardiac source is not possible with other ECG techniques.

NONINVASIVE HIS BUNDLE RECORDING. EXPERIENCE FROM THREE YEARS OF CLINICAL TRIALS

John J. Rozanski, MD, Agustin Castellanos, MD, FACC; Richard Luceri, MD, Barry R. Alter, MD, FACC; Richard G. Pozen, MD, Robert J. Myerburg, MD, FACC; VA Hospital and University of Miami, Florida

Non-invasive His bundle recordings (HBE) were performed in 55 consecutive patients (pts) also undergoing intracardiac HBE for various forms of conduction system disease to provide a study group with a wide variety of P-H and H-V intervals. Signal input noise discrimination, amplification, and averaging of 1024 cardiac cycles were performed. Clearly defined non-invasive HBE were obtained in 25/55 pts (45%). In this group correlations with invasive P-H and H-V intervals were good, r = +0.88 and +0.97, respectively. Failure to record a satisfactory HBE occurred in 30/55 (55%). Of these, prolonged atrial activity obscured the non-invasive HBE in 17/55 (31%). A short A-H likewise obscured the HBE in 5/55 (9%). In 8/55 (15%), a clear HBE could not be extracted from background noise, due in 4 pts to high impedence at one or more skin electrodes. Optimal lead location for recording the HBE varied from pt to pt: V_1, V_2, V_6 or V_1, V_4, V_9 were usually satisfactory locations. First degree AV block or A-H prolongation virtually assured detection of HBE (95%). Conversely, short A-H, short P-R, or intra-atrial conduction delay in the standard ECG made non-invasive HBE recording virtually impossible. In conclusion, an accurate non-invasive HBE can be recorded in most patients with first degree heart block or long A-H intervals. This HBE is reproducible and correlates well with invasively measured HBE.

PROGNOSIS AFTER INFARCT: STRATIFICATION BY Q WAVE EVOLUTION

Alan G. Wasserman, MD; Jorge C. Rios, MD; George B. Bren, MD; Richard J. Katz, MD; Daniel Bogaty, BS; Allan M. Ross, MD, FACC, For the Aspirin Myocardial Infarction Study Group, George Washington University, Washington, D. C.

Loss of ECG Q waves after myocardial infarction (MI) has been considered a sign of localized damage implying a favorable prognosis. We tested this hypothesis in the 4230 patients (pts) of the Aspirin Myocardial Infarction Study (AMIS). As aspirin vs placebo comparison showed no long-term mortality difference, data was pooled for both treatment groups. Follow-up averaged 38.2 months. There were 602 pts (14.2%) who had diagnostic Q waves at the time of MI but lost these Q waves by randomization. There was no difference in total mortality for pts losing Q waves (39/602, 6.5%) versus those with persistent single ECG defined infarct sites (205/2354, 8.7%, p=ns). Because stratification of pts by loss vs persistence of Q wave carried no prognostic value, further analysis was performed using the Minnesota Code for major, moderate or minor infarct pattern (based upon duration of Q's and Q/R ratio) and the distribution criteria for multiple site infarcts. Total mortality for single ECG defined infarct sites revealed a higher mortality in the major subgroup (106/999, 10.6%), than in the moderate (55/763, 7.2%, $p < .01$) or the minor subgroup (44/592, 7.4%, $p < 0.01$). Those pts with multiple ECG infarct sites also had a significantly higher mortality, 186/1274, 14.6% compared with those pts with single infarct sites, 244/2956, 8.2% $p < 0.02$.

Conclusion: 1) Q wave loss does not portend an improved prognosis; 2) Electrocardiographic criteria for extensiveness of infarct does identify subgroups with increased long-term mortality rates.

ELECTROCARDIOGRAPHIC "LOW VOLTAGE, ANTERIOR WALL MYOCARDIAL INFARCT PATTERN, ARRHYTHMIAS AND ABSENCE OF LEFT VENTRICULAR HYPERTROPHY"-THE CHARACTERISTIC ELECTROCARDIOGRAM OF AMYLOID HEART DISEASE FROM ANALYSIS OF 40 NECROPSY PATIENTS

Bruce F. Waller, MD, and William C. Roberts, MD, FACC, National Heart, Lung and Blood Institute, Bethesda, MD

Little information is available correlating the electrocardiogram (ECG) and necropsy findings in patients (pts) with cardiac amyloidosis (A). Thus, ECG's were reviewed in 40 pts with cardiac A. All ECGs were abnormal and all 40 hearts had A present in the right (R) and left (L) atria, R and L ventricular free walls and ventricular septae. All pts had clinical cardiac dysfunction. Clinical diagnosis of non-cardiac A had been made in 17 (43%) and a diagnosis of cardiac A in only 4 (10%). ECG findings were: low voltage in 38 (95%); myocardial infarct pattern in 38 (95%) (anterior=36 [95%], posterior=4 [11%]); arrhythmia in 36 (90%)(atrial=34 [89%], ventricular=25 [66%]); atrio-ventricular block in 31 (78%)(1° in 21 [53%], 2° in 5 [13%], 3° in 5 [13%]); abnormal QRS axis in 22 (56%)(R in 8 [20%], L in 14 [35%] and complete bundle branch block in 14 (35%)(R=8 [20%], L=6 [15%]). No pt had ECG voltage criteria for left ventricular hypertrophy (LVH) despite increased heart weights in all 40 (380 to 800 gms, mean=590) and a history of systemic hypertension in 20 (50%). Thus, in pts with cardiac dysfunction, in the absence of chest pain and valvular heart disease, low voltage, anterior wall infarct pattern, arrhythmia and absence of LVH on the ECG suggests cardiac A, and these findings are nearly diagnostic of cardiac A in pts with known non-cardiac A.

WEDNESDAY, MARCH 18, 1981
PM
SURGICAL MANAGEMENT OF CONGENITAL HEART DISEASE
2:00-3:30

PARTIAL ATRIOVENTRICULAR CANAL DEFECT IN ADULTS

John K. Hynes, MD; Abdul J. Tajik, MD, FACC; James B. Seward, MD, FACC; Valentin Fuster, MD, FACC; Donald G. Ritter, MD, FACC; Robert O. Brandenburg, MD, FACC; Francisco J. Puga, MD; Gordon K. Danielson, MD, FACC; Dwight C. McGoon, MD, FACC, Mayo Clinic, Rochester, MN.

Partial atrioventricular canal defect (PAVC) is rare in adults (≥20 years), hence little is known of the clinical profile, and surgical experience is limited. Between 1958-January 1980, 47 patients (pts) (28 females, 19 males) mean age 36 years (range 20-75) were seen; 15 pts (32%) were >45 years old. Thirty-seven were in functional Class I or II and 10 were in Class III or IV. Right bundle-branch block and left axis deviation were present in 43 pts (91%). Surgical repair was performed in 43 pts (4 declined surgery); 34 had preoperative catheterization. Mean Qp/Qs was 3.0, mean pulmonary artery pressure ≥25 mm Hg (range 25-50) in 8 pts. "Gooseneck" deformity of the LV outflow tract was not readily apparent in 3 pts on left ventriculography. Of the 9 noncatheterized pts, 8 had a correct preoperative diagnosis. Mitral cleft was sutured in 37 of 43 pts. Operative mortality was 7% (3 of 43 pts), with no operative deaths since 1975 (15 pts, 4 of them >50 years). Although mitral regurgitation was moderate to severe in 9 pts, only 2 had valve replacement. No complete heart block occurred. On follow-up of 3-269 months (mean 83) 2 deaths had occurred--at 3 months (mitral prosthesis malfunction) and 31 months (congestive heart failure). All survivors are in Class I or II. Five pts are on antidysrhythmic medication. No long-term survivor has required reoperation or pacemaker insertion. CONCLUSION: This is the first study detailing the clinical profile and management of a large group of adults with PAVC. Surgical repair in this age group can be performed at low risk and with gratifying long-term results.

LATE RESULTS OF CORRECTION FOR TETRALOGY OF FALLOT: A LONG-TERM, FOLLOW-UP EVALUATION OF 300 PATIENTS

Karl J. Karlson, MD; Michael Jones, MD; James S. Donahoo, MD; Catherine A. Neill, MD; J. Alex Haller, Jr., MD; Vincent L. Gott, MD, Johns Hopkins Hospital, Baltimore, Md.

To evaluate the potential for normal lifestyle late after repair for tetralogy of Fallot, we performed a follow-up evaluation of 300 consecutive patients (pts) undergoing operation from 1965-1975. Mean age at operation was 13 years (yrs) (1-35 yrs) and at follow-up 21 yrs. There were 29 (10%) early deaths. Late evaluations were performed at least 5 yrs and up to 15 yrs (mean 8 yrs) after correction by clinical examination (76%) and correspondence (24%). Of 271 early survivors, 88% were available for evaluation. Postoperative catheterizations were performed in 140 (59%). Late results were classified as good (no symptoms, no cardiac medications, RV pressure < 60 mmHg and/or < 50% Ao pressure, left-to-right shunt < 1.4/1.0, and an active lifestyle); fair (any activity restriction, any cardiac medication, any arrhythmia except RBBB, any right-to-left shunt, and/or valvar regurgitation); or poor (reoperation, severe activity restriction, RV pressure = Ao pressure, heart block, and/or severe valvar regurgitation). Good results were present in 156 (66%), fair results in 47 (20%), and poor results in 21 (8%). Reoperation was required in 14 (6%); no deaths occurred. There were 14 (6%) late deaths: 9 sudden, 3 from failure, 1 from endocarditis, 1 from cerebral embolus. Actuarial survival is 87% at 5 yrs (n=271), 83% at 10 yrs (n=183), and 77% at 15 yrs (n=24). Actuarial probability of obtaining a good or fair result is 79% at 5 yrs, 74% at 10 yrs, and 60% at 15 yrs. At follow-up in 48 pts < 14 yrs of age, mean height ↑ 13 %ile and weight ↑ 19 %ile. Of 138 pts > 18 yrs of age, 25% are married and 51% are employed. Thus, most pts with tetralogy of Fallot may anticipate satisfactory late results.

A FIVE YEAR FOLLOW-UP OF AORTIC HOMOGRAFT MONOCUSPS USED IN RECONSTRUCTION OF THE RIGHT VENTRICULAR OUTFLOW TRACT IN INFANTS WITH TETRALOGY OF FALLOT.

Rosemary Radley-Smith, Charles Ilsley, Colin Reid and Magdi Yacoub, Harefield Hospital, London, U.K.

A monocusp of a fresh adult-sized antibiotic sterilised aortic homograft was used to enlarge the pulmonary valve ring and to render the valve competent in fourteen infants under the age of 2 years undergoing primary total correction of Tetralogy of Fallot. Their ages were 4-24 months. These children have now been followed up for a minimum period of 5 years (5 - 8.1 years) mean 6.15 years. All are asymptomatic and not on cardiac drugs. Five patients (35%) have developed a grade I-II early diastolic murmur 0.4 years after operation, with no significant increase in heart size on chest radiograph. All patients have been routinely reinvestigated 2 weeks - 54 months after operation. Seven have been reinvestigated again at least 2 years after the initial restudy. Thirteen patients had a RVOT gradient of less than 15mmHg and the RV/LV ratio was less than 0.4 in 12. The RVEDP was less than 12 mmHg. In the patients reinvestigated twice there was no significant change in RVOT gradient, RV/LV ratio or RVEDP. There is no angiographic evidence of severe pulmonary regurgitation.

It is concluded that monocusps used in the reconstruction of the RVOT in patients with Tetralogy of Fallot operated upon under the age of 2 years appear to allow for growth and give good long-term results.

MUSTARD'S OPERATION IN THE FIRST MONTH OF LIFE

Leonard L. Bailey, MD, FACC, John G. Jacobson, MD, FACC, William H. Merritt, MD, Robin W. Doroshow, MD, and Eugene L. Petry, MD, Divisions of Cardiovascular Surgery and Pediatric Cardiology, Loma Linda University, Loma Linda, California 92350.

Since April 1976, Mustard's interatrial baffle procedure has been accomplished in seven newborns with Transposition of the Great Arteries (TGA) under one month of age who were persistently symptomatic following Rashkind's balloon atrioseptostomy. Two had associated large ventricular septal defects (VSD) patched at the time of physiologic correction. Average age was 11 days (36 hrs. - 28 days). Weight averaged 3.4 kilograms (2.7 - 4.2). All were done using deep hypothermic circulatory arrest, averaging 65 minutes (48-87 minutes) at a mean core temperature of 12.5° C. A mean of 2.8 days of post-operative ventilatory assistance was required. One death occurred in a 28 day-old male with associated VSD who, the morning after surgery, developed sudden unresponsive cardiac standstill. Post-operative hospitalization averaged 15 days (10-23 days). Follow-up evaluation has extended from 3 to 56 months, averaging 34.3 months. Five patients have been re-studied 10-21 months post-operatively. One had obstruction of the superior limb of the baffle which had separated from the right atrial wall permitting a modest right to left shunt. She has had uneventful repair employing a unique modification of Senning's operation. Another child has assymptomatic partial obstruction of the superior limb of the baffle demonstrated angiographically. No other intracardiac shunts have been identified. None have pulmonary venous obstruction and all are in prevailing normal sinus rhythm. Early correction of persistently symptomatic neonates with TGA with or without VSD has obviated the need for palliative operations and produced gratifying early and late results.

COMPLETE ATRIOVENTRICULAR CANAL ASSOCIATED WITH TETRALOGY OF FALLOT

Gideon Uretzky, MD; Francisco J. Puga, MD; Robert H. Feldt, MD, FACC; Paul R. Julsrud, MD; William D. Edwards, MD; Gordon K. Danielson, MD, FACC; Dwight C. McGoon, MD, FACC; Mayo Clinic and Mayo Foundation, Rochester, Minn.

The surgical repair of complete atrioventricular canal associated with tetralogy of Fallot has been reported in a few cases. Between 1969-1979, a total of 14 patients with the combination of complete atrioventricular canal (13 type C, and 1 type B), associated with tetralogy of Fallot, had repair of both anomalies. Patient age ranged from 1 to 12 years. Five had a previous shunt operation, 13 had combined subpulmonary and valvular stenosis and 1 had subpulmonary stenosis only. Six patients had Down's syndrome. Eleven (79%) had associated anomalies including left superior vena cava (3), right aortic arch (2), atrial septal defect secundum type (7), patent foramen ovale (1), anomalous left anterior descending coronary artery (1), and aberrant right subclavian artery (1). The precise preoperative diagnosis was established in 10 (71%) by angiography showing the characteristics of tetralogy of Fallot on RV angiogram and those of atrioventricular canal on LV angiogram. In 4 of these patients the diagnosis was supported by two dimensional echocardiography. The typical features of the condition include anterior displacement of the infundibular septum and "goose neck" LV outflow changes. Surgical repair is complex. The repair of the ventricular septal defect, with its large anterior subaortic extension required a combined atrial and right ventricular approach in 4 patients. Outflow tract reconstruction (transanular patch) was performed in 9 patients. The hospital mortality rate was 21%, and there were two late deaths. Nine (64%) patients are still living having a satisfactory result.

CONDUIT SURGERY FOR RIGHT VENTRICULAR AND PULMONARY ARTERY CONTINUITY. EXPERIENCE IN BOTH INFANTS AND OLDER CHILDREN.

Constantine Mavroudis, MD; Kevin Turley, MD, FACC; Paul A. Ebert, MD, FACC; University of California, San Francisco, CA 94143.

The conduit repair (Rastelli) of lesions requiring reconstitution of right ventricular (RV) to pulmonary artery (PA) continuity has been demonstrated effective. Serious questions have arisen as to the longevity of such conduit replacements with degeneration of the valve components and the development of gradients at both the anastomotic, conduit, and valvular levels. These are of special import in the infant group. During the period June 1, 1975-July 1, 1980, 110 RV to PA conduit repairs were performed at University of California, San Francisco. Ages ranged from 14 days to 35 years, median 15 months. Lesions included truncus arteriosus, transposition of the great arteries with ventricular septal defect, tetralogy of Fallot and pulmonary atresia. Conduit size ranged from 12 to 22 mm, median 14 mm. Overall operative survival was 80%. Special risk factors identified included absence of pulmonary arteries, associated lesions (i.e. interrupted arch, valvular insufficiency requiring replacement) and age < 6 weeks. When such patients were excluded, survival was 90%. 10 conduit replacements were undertaken at a mean of 27 months in follow-up, while 100 patients from 3 months to 68 months postop. remain at risk. Operative survival in repaired patients in whom replacement was necessary was 100%. Conduit repair of RV to PA discontinuity results in stimulation of symmetrical anatomic growth and hemodynamic repair. Reoperation is necessary in these patients in response to both this growth and the intrinsic problems of valvular degeneration and pseudointimal proliferation associated with current conduits, but replacement is possible with low risk.

WEDNESDAY, MARCH 18, 1981
PM
EXERCISE PHYSIOLOGY AND TRAINING
2:00-3:30

DECREASED MYOCARDIAL OXYGEN DEMAND FROM EXERCISE TRAINING SECONDARY TO IMPROVED WORK EFFICIENCY: EFFECT OF HABITUATION VERSUS AEROBIC CONDITIONING

Rudolph H. Dressendorfer, PhD; Joan L. Smith, MA; Ezra A. Amsterdam, MD, FACC, Human Performance Lab, University of California, Davis, California.

Exercise training (ExT) in coronary patients (pts) has been shown to improve aerobic capacity, as measured by an increase in total body maximal oxygen consumption ($\dot{V}O_2$ max), and to decrease myocardial oxygen demand ($M\dot{V}O_2$) during submaximal Ex. The lowering of $M\dot{V}O_2$ with Ex at the same external workload after training most often results from utilization of a decreased percentage of $\dot{V}O_2$max because of greater aerobic capacity. Our purpose was to determine whether $M\dot{V}O_2$ during submaximal walking Ex could be reduced by improving work efficiency without a concomitant increase in $\dot{V}O_2$max. The pts were 8 men with ischemic heart disease who did not have symptom-limitations on maximal Ex testing. ExT was restricted to fast walking since jogging caused ischemic ST-segment depression. Walking speed was individually prescribed between 3.4 to 4.7 mph in order to maintain the heart rate (HR) x systolic blood pressure product just below the ischemic threshold. After 14 to 20 wks of ExT 3 x per wk, directly measured $\dot{V}O_2$max was not significantly changed. However, significant ($P < .05$) reductions in HR (120 to 108 beats/min), rate-pressure product (195 to 162 x 10^2), total body $\dot{V}O_2$ (20.0 to 18.2 ml/kg/min) and perceived exertion were found after ExT when the pts walked at their prescribed speeds. Total body $\dot{V}O_2$ during submaximal Ex was reduced secondary to habituation, i.e., enhanced work efficiency. Consequently, estimated $M\dot{V}O_2$ was significantly lower after ExT due to decreased peripheral oxygen demand, and not because of a reduction in the relative workload. Coronary pts may benefit from regular Ex even when aerobic capacity is not increased.

DAILY EXERCISE AUGMENTS ANTEGRADE FLOW FOLLOWING PARTIAL CORONARY OCCLUSION

Ming Hwang, MD, FACC; Alan Gabster, MD; Henry Loeb, MD, FACC; Rolf Gunnar, MD, FACC, Loyola University Medical Center, Maywood, Il and VA Hospital, Hines Il

Previously we showed that dogs subjected to daily treadmill exercise (45 min, 4-6 mph, 10° slope for 4-6 weeks) increased subendocardial blood flow (SEF) in an area supplied by partial (80-90%) circumflex artery occlusion ($P\text{-}CF_xO$) when compared to similar dogs not exercised. All visible epicardial collaterals were ligated. To determine if the increased flow was across the partial constriction or from collaterals, 22 dogs were prepared as above. Posterior SEF was measured after $P\text{-}CF_xO$ and after total circumflex occlusion (TCF_xO) to assess the proportion SEF which was antegrade. Results: In 6 experiments, PSEF measured immediately after PCF_xO averaged .74±.20 ml/min/gm (Mean ± SEM) falling to .10±.03 ml/min/gm upon TCF_xO ($p<.001$). In 16 dogs, PSEF measurements were made 4-6 weeks after PCF_xO. Eight dogs remained sedentary and 8 underwent daily exercise. In the 8 sedentary dogs, PSEF with PSF_xO averaged .94±.12 ml/min/gm falling to .64±.11 ml/min/gm upon TCF_xO (NS). In the 8 exercised dogs, PSEF with PCF_xO averaged .95±.15 ml/min/gm falling to .38±.15 ml/min/gm after TCF_xO ($p<.05$). Conclusion: Immediately following PCF_xO, PSEF depends primarily on antegrade flow. After 4-6 weeks, retrograde collateral flow makes a significant contribution to PSEF in sedentary dogs. Dogs subjected to daily exercise following PCF_xO have a very significant increase in the proportion of blood flowing antegrade across the PCF_xO. Therefore, daily exercise seems to enhance antegrade flow in PCF_xO dogs. It is proposed that this enhanced antegrade flow is due to an effect of daily exercise on myocardial vascular resistance.

DOES LV FUNCTION REACH A STEADY STATE DURING SUSTAINED EXERCISE?

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Exercise (Ex) studies often assume that a hemodynamic steady state is reached in 3 min. Eleven asymptomatic males 4 to 6 years post aorto-coronary bypass did supine Ex at 450 KPM/min for 3-6 min (mean 5.3). Cardiac output (CO), heart rate (HR), stroke volume (SV), ejection fraction (EF), and circumferential shortening velocity (VCF) were measured by computer assisted analysis of the motion of implanted midwall markers.

RESULTS:	CO	HR	SV	EF	VCF
	l/min	beats/min	ml	%	circ/sec
CONTROL	5.6(1.6)	67(10)	84(21)	48(4)	.61(.16)
Ex min 1	8.6(2.3)*	99(13)*	87(23)	50(6)	.85(.20)*
Ex min 3	9.8(2.2)*	112(13)*	89(22)	50(7)	.94(.26)*
PEAK CO	10.9(2.7)*	118(13)*	93(26)*	53(7)*	1.03(.28)*

mean (SD); Ex versus CONTROL *$p<0.01$

CO increased by 75% ($p<0.01$) between control and 3min Ex and by 25% ($p<0.01$) between 3 min and end Ex. This increase was primarily accounted for by an increase in HR with a lesser contribution by SV. Over 85% of the heart rate change occurred within the first 3 min whereas over 40% of SV and 60% of EF increases occurred after 3 min. We conclude that steady state cardiac output and LV function is often not reached within 3 min. Cardiac output may continue to rise later in exercise due to late increases in EF and SV probably due to circulating catecholamines.

ENHANCED OXYHEMOGLOBIN DISSOCIATION CONTRIBUTES TO UNLOADING OXYGEN AT REST AND DURING EXERCISE IN SEVERE CHRONIC HEART FAILURE PATIENTS

Mark Nemerovski, MD; Stanley A. Rubin, MD, FACC; Harvey Brown, MD; David Mickle; H.J.C. Swan, MD, PhD, FACC, Cedars-Sinai Medical Center, Los Angeles, California

Maximum oxygen transport is abnormally low in heart failure. Therefore, we studied the potential mechanisms for increased unloading of oxygen in 15 chronic heart failure pts at rest (R) and during maximum cycle ergometry (E). We measured cardiac index (CI) by thermodilution, oxygen consumption (VO_2) by expired air analysis, mixed venous pO_2 and pH by electrodes and oxyhemoglobin saturation (S) by oximetry. Arteriovenous O_2 difference ($AV\text{-}O_2$) and P_{50} (pH=7.4, T=37°C) were calculated. At R, CI was 1.8±0.31/min/m^2 (mean±SD) and rose slightly but significantly during E to 2.4±0.7, ($p<0.01$). At R, VO_2 was 140±20 ml/min/m^2 and rose substantially during E to 290±80 ($p<0.01$). At R, $AV\text{-}O_2$ was 8.1±1.8 ml/100 ml and rose substantially during E to 12.5±3.4 ($p<0.01$). At R, mixed venous pH (MVpH) was normal (7.4±0.05) and therefore made no contribution to enhanced oxyhemoglobin dissociation (OHD). However, P_{50} was increased to 29.8±3.5 torr (normal 26.9 torr, $p<0.01$), accounting for 16% of peripheral O_2 consumption ($AV\text{-}O_2$). At E, P_{50} remained elevated at 30.9±5.8 torr. In addition, however, MVpH was decreased to 7.34±0.06 ($p<0.05$ cf. control) causing a further shift in OHD by the Bohr effect. At E, enhanced OHD also accounted for about 15% of the $AV\text{-}O_2$. After vasodilator therapy (hydralazine or minoxidil), R and E MVpH were 7.44±0.03 and 7.37±0.04 and P_{50}s were 27.2±1.5 and 27.9±1.8 torr respectively. We conclude that peripheral O_2 consumption in the chronic heart failure patient depends in part on a shift in OHD, and is less dependent on this compensatory mechanism after vasodilator therapy.

CHANGES IN LEFT VENTRICULAR VOLUMES DURING UPRIGHT EXERCISE IN PATIENTS WITH CORONARY ARTERY DISEASE

Abdulmassih S. Iskandrian, MD, FACC, A-Hamid Hakki, MD, Bernard L. Segal, MD, FACC and Sally A. Kane, RN. Cardiovascular Institute, Hahnemann Medical College and Hospital, Philadelphia, Pennsylvania.

We studied 24 patients (pts) with coronary artery disease (CAD) using symptom-limited upright exercise (EX) on a bicycle ergometer. First-pass radionuclide angiograms were obtained at rest (R) and peak EX. Fifty percent of the pts had previous transmural infarctions (MI). Twelve normal men (NL) served as a control. Nine pts developed angina or ST depression during EX. The EX heart rate (HR) and EX tolerance were lower in pts than normal ($p < .01$).

	LV-EDV (ml)		SV (ml)		CO (L/min)		LV-EF	
	R	EX	R	EX	R	EX	R	EX
No MI	174±41	185±40	95±25	90±32	7.2±2.6	*12.7±5.3	55±10	*49±12
MI	229±99	253±98	76±25	89±35	4.9±1.3	*10.2±2.7	38±13	38±12
NL	150±28	170±35	92±15	*125±20	7.5±0.9	*19.8±3.9	62±6	*75±5

{LV, left ventricle; EDV, end-diastolic volume measured by area-length method; SV, stroke volume; CO, cardiac output; EF, ejection fraction; *, $p < .01$, R vs EX}. Six NL and 12 pts had ≥ 10% increase in EDV during EX. The remaining had either no change or decrease. Pts with MI had higher EDV at R and EX than NL ($p < .01$). However, there was no significant difference between R and EX-EDV (and the change in EDV during EX) in NL compared to pts (with or without MI). The SV, CO and EF were higher in NL than pts with CAD during EX ($p < .01$). We conclude: There are significant differences in the SV, CO, HR and EF between NL and pts with CAD during upright EX. However, LV dilatation is neither sensitive (50%) nor specific (50%) for CAD. Moreover, LV dilatation is not affected by the resting EF or by presence of previous MI.

ALTERATIONS IN PLASMA LIPOPROTEIN LEVELS DURING HIGH MILEAGE RUNNING

Rudolph H. Dressendorfer, PhD; Charles E. Wade, PhD; Conrad Hornick, PhD; Ezra A. Amsterdam, MD, FACC, Human Performance Laboratory, University of California, Davis and Tripler Army Medical Center, Honolulu, Hawaii.

Effects of long-distance running on plasma lipoprotein levels were studied using twelve male marathon runners, mean age 40, who ran on the average of 17.3 mi/day for ten days, rested for 70 hr, then continued to run for eight more days. Body weight and percentage body fat were unchanged despite an estimated caloric intake of 4800 kcal/day. Blood samples were obtained on eight mornings prior to running. No significant change in total cholesterol (C) or low density lipoprotein-C was found. Compared to control values, high density lipoprotein (HDL)-C increased 18% and triglycerides (TG) decreased 22% after one week of running, and the observed changes were inversely correlated. The 70-hr rest period disrupted this significant rise in HDL-C and fall in TG. However, with continued running HDL-C and TG returned to pre-rest period values. The findings suggest that increased HDL-C with exercise training is coupled to the mechanism which lowers plasma TG. More importantly, detraining effects on plasma HDL-C and TG may be observed within days of stopping exercise when caloric intake remains high.

WEDNESDAY, MARCH 18, 1981
PM
HYPERTENSION—THEORY, EXERCISE TESTING, VASCULAR REACTIVITY, DIASTOLIC ABNORMALITY
2:00-3:30

EFFECT OF BETA BLOCKADE THERAPY ON HYPERTENSIVE CARDIAC HYPERTROPHY

M.Mohsen Ibrahim,MD,FACC; M.Aziz Madkour,MB,BCh Ragaa Mossallam,MB,BCh, University of Cairo and Cairo Transport Organization,Cairo,Egypt.

The effect of B-blockade therapy on LV mass(LVM) has not been studied in hypertensive patients. Studies in animals have shown that certain anti-hypertensive drugs reduce cardiac hypertrophy. Atenolol(A)- a cardioselective beta blocker with no intrinsic sympathomimetic activity- was given(100mg/d) for 8 weeks to 17 male patients with essential hypertension (mean age 49y) and without evidence of other cardiac disease. Echocardiographic dimensions (ED)and urinary epinephrine(UE) were determined after 4 weeks placebo and after A therapy. ED were measured in 16 age matched normotensive males. Septal(S) and posterior wall(PW) thickness(T),LVM index(LVMI),ratio of LVWT to radius(h/r),UE and mean circumferential wall stress (MCS) were all significantly increased($p < 0.01$) in hypertensive patients. Following A blood pressure(BP) decreased from 197/119 ± 5.7/3.9(mean ± SE) to 160/98 ± 2.9/2.3 mmHg($p< 0.001$), ST from 11.1 ± 0.5 to 10.4 ± 0.4 mm ($p <0.05$), LVMI from 126 ± 10.1 to 112 ± 8.5 gm/m^2 ($p <0.005$), MCS from 342 ± 20.1 to 264 ± 17 $10^3 dynes/cm^2$ ($p <0.001$), end diast.diameter(EDD) from 51.9 ± 1.3 to 50.8 ± 1.4 mm ($p < 0.05$) and UE from 149 ± 9.6 to 91 ± 4.4 mcg/24hs.($p <0.001$). PWT and h/r did not change. Δ LVMI was significantly related to Δ MCS($r = 0.42$),poorly related to Δ syst.BP($r = 0.32$)and Δ UE($r = 0.22$)and not related to Δ diast.BP($r = 0.03$). CONCLUSION:1.A produced a rapid decrease in LVM,however,some of the changes might be due to a decrease in EDD since h/r did not change.2.Regression of cardiac hypertrophy appears to be more dependant on reduction in wall stress than a direct hypotensive effect of therapy or decrease in adrenergic activity (UE).

EFFECTIVE AND SAFE TREATMENT OF HYPERTENSIVE CRISIS WITH NIFEDIPINE.

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The present management of hypertensive crisis with nitroprusside, diazoxide or hydralazine requires close monitoring of blood pressure (BP) and dose of the administered drug due to possible side effects.
We investigated the effectiveness and safety of nifedipine to patients with hypertensive crisis. Twenty milligrams nifedipine were given orally to 7 pts. suffering from a marked rise of blood pressure of > 25o mmHg systolic and >14o mmHg diastolic as well as typical clinical manifestations (headache, nausea, visual loss, restlessness and confusion). Blood pressures were measured by the method of Riva Rocci. Blood pressure and heart rate were taken 2o, 1o minutes and immediately before application and 1o, 2o, 3o, 45, 6o and 9o minutes later. Results (mean ± SD) were as follows:

	-2o	-1o	o	1o	2o	3o	45	6o	9o min.
syst. BP	272 32	256 26	257 4o	237 28	179 28	177 27	177 22	176 25	176 28
diast. BP	159 18	158 1o	157 13	147 9	121 16	1o5 15	1o2 14	98 19	1o4 13
HR	69 17	68 17	71 16	64 19	74 19	77 19	74 18	74 19	73 17

Nifedipine caused in all patients a prompt decrease of the elevated blood pressure. Its onset was within 1o minutes and reached the maximal effect by 3o minutes. The drop of blood pressure was concomitant with a marked improvement of symptoms. Of importance, there were no signs of overshoot or tachycardia. Therefore, nifedipine appears to be both a safe and effective drug in the management of acute hypertensive crisis.

EVIDENCE FOR ALTERED VASCULAR REACTIVITY IN YOUNG SUBJECTS WITH LABILE, BORDERLINE HYPERTENSION

Jay M. Sullivan, MD, FACC; Darrell R. Patrick, BS; Steve W. Reed, MD; Ahmad Banna, MD; John C. Riddle, MD; Collier Jordan, MD, University of Tennessee, Memphis, TN

Forearm hemodynamics were measured by venous occlusion plethysmography during periods of ad lib diet, 10 mEq sodium diet and 200 mEq sodium diet in 15 normal subjects (NL) and 15 subjects with labile, borderline hypertension (BBP). The two groups did not differ significantly in regard to age, sex or race. Average resting blood pressure (BP) in the normal group was 110/74 and 122/85 in the BBP group ($p<.005$). Resting forearm blood flow (FBF), forearm vascular resistance (FVR), venous compliance (VC) and capillary filtration coefficient (CFC) did not differ significantly between the two groups. In both groups, diastolic blood pressure was highest when first measured during the ad lib state (81 mmHg) and lower during the 10 mEq (79 mmHg) and 200 mEq (78 mmHg) sodium state ($p<.01$). Venous capacitance was lowest during the ad lib state, 0.50 vs 0.70 and 0.57 ml/min/mmHg/100 g x 10^4 ($p<.05$). In the normal group, the 10 and 200 mEq sodium diets had little effect on forearm hemodynamics. Sodium depletion brought out a difference between the NL and BBP subjects. The FVR of the BBP subjects rose significantly during salt depletion, 35.9 vs 60.9 mmHg/ml/min/100 g ($p<.05$) while that of the NL subjects did not. Sodium sensitivity was arbitrarily defined as an increase in mean blood pressure of more than 5% when sodium repleted. The individuals who were salt sensitive had a higher FVR during sodium depletion than those who were salt resistant, 64.9 vs 44.6 mmHg/ml/min/100 g ($p<.03$). We conclude that young individuals whose resting diastolic BP intermittently rises above 90 mmHg already have alteration in vascular reactivity.

DIASTOLIC VENTRICULAR ABNORMALITY IN HYPERTENSIVE HEART DISEASE: ATRIAL EMPTYING INDEX

Gerald R. Dreslinski, MD; Edward D. Frohlich, MD,FACC; Francis G. Dunn, MD; Franz H. Messerli, MD,FACC; Daniel H. Suarez, MD; Efrain Reisin, MD. Ochsner Medical Institutions, New Orleans, LA.

Left ventricular (LV) diastolic properties in hypertensive heart disease were analyzed, employing the atrial emptying index (AEI), thereby assessing the rapid phase of LV diastolic filling. 10 normal subjects (Group 1), 11 hypertensive patients without evidence of cardiac involvement (Group 2), and 9 hypertensive patients with ECG and/or echocardiographic evidence of LV hypertrophy (Group 3) were studied by concomitant M-mode echocardiography and systemic hemodynamics. Whereas cardiac index (dye dilution), and fiber shortening rate (V_{cf} by echocardiogram) were similar in all three groups, there was a progressive increase in left atrial index (LAI) (1.30 vs 1.74 and 1.30 vs 1.84 cm/m^2, Group 1 vs Group 2 and Group 3, respectively; $p<0.001$), and a progressive decrease in AEI (0.82 vs 0.63, $p<0.001$, Group 1 vs Group 2, and 0.82 vs 0.60, $p<0.02$, Group 1 vs Group 3). No correlation existed between the AEI and the LAI, mean arterial pressure, or total peripheral resistance, in these three groups.

These data suggest that the LV is less compliant early in hypertension, before ECG, anatomic or LV systolic echocardiographic abnormalities are detectable. AEI, therefore, appears to be an early indicator of abnormalities of LV diastolic compliance, thus far the earliest sign of cardiac involvement in hypertensive disease.

XERCISE TOLERANCE TESTING IN ADOLESCENTS WITH ESSENTIAL /PERTENSION

rthur A. Klein, MD, FACC; Wallace W. McCrory, MD; lchard Rosenthal; Mary Allen Engle, MD, FACC
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Exercise tolerance was evaluated in racially heterogeneous age-matched adolescent males with essential hypertension (EH) (5), with labile hypertension (LH) (14) and normal blood pressure (NC) (15). All completed 12 minutes on the treadmill (Bruce protocol). Test normals did not differ significantly from our lab normals. Heart response follows:

	AGE (YRS)	BASE-LINE	p vs NORM	MAX	p	2 MIN REST	p	5 MIN REST	p
C	16.7	80±16		167±16		93±17		87±13	
H	16.4	86±11	NS	172±12	NS	108±16	<.01	98±12	<.01
H	15.1	77±14	NS	184±15	<.05	122±28	<.055	108±18	<.005

Lactate levels, sampled from an indwelling venocath. ere:

	BASELINE	p vs NORM	MAXIMAL EXERCISE	p vs NORM
C	11.7±3.9		25.9±8.4	
H	15.5±4.3	<.02	40.4±14.6	<.002
H	16.1±5.1	<.05	43.5±17.3	<.005

We conclude, unlike previously reported data, that 1) EH is associated with higher heart rate response to xercise; (2) both EH and LH differ from NC with a prolonged exercise recovery phase that is most marked in EH; 3) EH and LH also appear to exercise less efficiently as videnced by elevated maximal exercise lactate levels.

K-421: A NEW ORAL ANGIOTENSIN CONVERTING ENZYME INHIBITOR FOR ESSENTIAL HYPERTENSION

oger K. Ferguson, MD, FACC; Peter H. Vlasses, PharmD; rian N. Swanson, PhD; David J. Cooper, MD; Richard O. avies, MD, FACC; William B. Abrams, MD, FACC, Thomas efferson University Hospital, Philadelphia, Penn.

The antihypertensive efficacy of MK-421 (N-[(S)-(ethoxycarbonyl)-3-phenyl-propyl]-L-alanyl-L-proline), a new ngiotensin converting enzyme inhibitor, was evaluated in 1 patients (6 men, 5 women), aged 31-69 years, with uncomplicated mild to moderate essential hypertension. The urpose of the study was to determine an effective dose or subsequent chronic administration. The patients were ospitalized after 2 weeks off all drugs. After 3 days n a 150 mEq Na^+, 80 mEq K^+ diet, mean (±S.D.) sitting lood pressure (BP) was 158/99 ± 11/10 mm Hg and upright lasma renin activity (PRA), 2.2 ± 1.1 ng/ml/hr, plasma aldosterone (PA), 17 ± 8 ng/dl and angiotensin I (AI), 0.51 ± .2 ng/ml. Alternating with placebo, MK-421 was given in ingle daily rising doses (2.5, 5 and 10 mg) depending on he presence and duration of a BP response (decrease in iastolic BP ≥ 10 mm Hg). PRA, PA and AI were measured at , 4, 8, 12 and 24 hr after placebo and each dose of K-421; BP was measured with an automatic device (Dinaap®) at frequent intervals up to 15 hours. After each ose of MK-421, though the mean maximal decrease in diatolic BP was similar (17-21 mm Hg), the mean onset (3.5 o 2 hr) and duration (7 to >13 hr) of the BP response aried with increasing dosage; 2 patients responded for :12 hr at 5 mg and 9, at 10 mg. Mean PRA increased, PA ecreased and AI did not change. Neither the magnitude or the duration of BP response correlated with baseline RA. No adverse effects occurred. Thus, in this study, K-421 proved to be a potent and effective antihypertensive agent with a dose-related onset and duration of effect.

WEDNESDAY, MARCH 18, 1981
PM
ECHOCARDIOGRAPHY: EXPERIMENTAL AND CLINICAL STUDIES
2:00-3:30

TRANSMISSION OF ECHOCARDIOGRAPHIC CONTRAST THROUGH THE LUNGS.

Richard S. Meltzer, MD; Charles T. Lancée, MSc; Otto E.H. Sartorius; Piet D. Verdouw, PhD; Patrick W. Serruys, MD; Catharina E. Essed, MD and Jos Roelandt, MD, FACC, the Thoraxcenter, Erasmus University and University Hospital, Rotterdam, the Netherlands.

Previous reports of transmission of echocardiographic contrast through a normal pulmonary capillary bed have all been based on pulmonary wedge injections. More proximal-ultimately peripheral-injections would be preferable. We tested two methods of transmitting echocardiographic contrast through the pulmonary capillary bed using injections proximal to the wedge position. We also tested the potential toxicity of echo transmission through the lungs using wedge injections. Method 1: hydrogen peroxide (H_2O_2) was injected in the right heart (RH) in 11 pigs. Method 2: diethyl ether was injected in the RH in 9 pigs. Left heart echo contrast was monitored in pigs by epicardial transducers. Method 3: saline was injected in the pulmonary wedge position in 8 rabbits. They were sacrificed 1 day later and examined for evidence of toxicity. Results - Method 1: nine pigs had left heart echo contrast after 1.5% or higher concentrations of H_2O_2. Ten had ECG changes and/or hypotension after H_2O_2. Method 2: seven pigs had left heart echo contrast after ether. Method 3: there was no definite injury in the lung from wedge injections. Three rabbits had small myocardial infarctions and 1 rabbit had a large infarct and died prior to sacrifice. We conclude that transmission of echocardiographic contrast through the lungs is potentially dangerous. Not only pulmonary wedge injections, but also more proximal wedge injections of selected substances may yield left heart echo contrast in experimental animals. Threshold concentrations of H_2O_2 may be found above which RH injections yield left heart echo contrast.

TRANSMISSION OF ECHOCARDIOGRAPHIC CONTRAST THROUGH THE LUNGS. II : HUMAN STUDIES.

Patrick W. Serruys, Richard S. Meltzer, Jackie McGhie, Jos Roelandt.
The Thoraxcenter, Erasmus University and Dijkzigt Hospital, Rotterdam, the Netherlands.

Pulmonary wedge injections (PWI) have been shown to cause left heart echocardiographic contrast (LHEC). In order to study factors affecting the success of this procedure, hand PWI of 10 cc 5% dextrose were performed in 41 patients (pts) and monitored by two-dimensional echocardiography. Swan-Ganz catheters alone were used in 3 pts, Cournand catheters alone in 27 pts, and both in 11 pts. Ten pts had angiograms during PWI of a non-ionic X-ray contrast agent in the same catheter position used for the echo study. Results : LHEC occurred in 3/14 pts with Swan-Ganz PWI and 30/38 pts with Cournand PWI. Pressure proximal to the catheter was ⩾ 300 mmHg when LHEC was seen. The 2 of 10 pts with retrograde X-ray contrast flow around the catheter failed to achieve LHEC after PWI. No complications occurred. After catheterization, 1/13 pts had an elevated LDH, 3/11 had localized lung scan defects, and 0/11 had localized chest film lesions. We conclude :

1) PWI can yield LHEC,
2) the success of this procedure varies with the type of catheter used,
3) a sufficiently occlusive wedge position must be attained to allow transmission of pressure to the capillary bed if LHEC is to be attained, and
4) the safety of this procedure needs further evaluation.

ULTRASONIC DETECTION OF THE ALTERED ACOUSTIC PROPERTIES OF MYOCARDIUM CHARACTERISTIC OF ADRIAMYCIN-INDUCED CARDIOMYOPATHY

Randolph D. Cohen, MD; James W. Mimbs, MD, FACC; Matthew O'Donnell, PhD; James G. Miller, PhD; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Missouri

To determine whether altered acoustic properties of the heart provide criteria potentially diagnostic of cardiomyopathic changes, we subjected 25 rabbits to prolonged administration of Adriamycin (1.2 mg/kg twice weekly). Rabbits were sacrificed at selected intervals from 10 to 18 weeks after the onset of administration of the drug and their hearts analyzed ultrasonically and chemically. Regional ultrasonic backscatter and collagen content, based on hydroxyproline, were assessed. Backscatter was measured with a frequency averaging procedure (integrated backscatter) to minimize phase cancellation and with an independent method employing spectral display (over the frequency range of 1 to 11 MHz) from which backscatter at 2.25 MHz could be calculated. Cardiac collagen content was significantly increased in fibrotic and myopathic zones of hearts from treated animals as compared to controls ($p < .05$). Integrated backscatter was markedly increased (by > 500%) in fibrotic regions and significantly, although less markedly, in regions without marked collagen deposition in myopathic hearts. Backscatter at 2.25 MHz was significantly increased (by > 600%) in fibrotic regions. Thus, alterations in acoustic properties occur in cardiomyopathic tissue, can be readily detected with reflected ultrasound, and provide a promising criteria for clinical diagnosis and characterization of evolution of cardiomyopathy due to Adriamycin and potentially other etiologies as well.

EMBOLIC POTENTIAL OF LEFT VENTRICULAR THROMBUS (LVT) DETECTED BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY (2DE)

J. Mark Haugland, MD; Richard W. Asinger, MD; Frank L. Mikell, MD; K. Joseph Elsperger, CCPT; Morrison Hodges, MD, FACC. Hennepin County Medical Center and the University of Minnesota, Minneapolis, MN.

LVT is a frequent complication of acute myocardial infarction, congestive cardiomyopathy, and left ventricular aneurysm. Routine 2DE evaluation of such patients may reveal clinically unexpected thrombus, since embolic phenomena may not have occurred. In considering anticoagulation, it would be useful to determine if any 2DE characteristics of LVT are associated with embolization.

We reviewed clinical and echocardiographic features of 49 patients with LVT diagnosed by 2DE. Twelve of these 49 (24%) had evidence of peripheral embolization. Multiple 2DE characteristics were analyzed, and several were associated with a high risk of embolization: 14 patients had free intracavitary motion (FIM) of a thrombus margin, and 8 (57%) had emboli. Thirty patients had LVT which protruded into the left ventricular cavity, and 8 (26%) had emboli. In contrast, only 1 of 16 patients (6%) with a flat mural LVT and no FIM embolized. Four of 12 patients (33%) with an aneurysm distorting the diastolic contour of the left ventricle had evidence of embolization.

Clinical features also appeared helpful. Eight of 28 patients (24%) with recent (< 3 weeks) infarction had evidence of embolization in contrast to 2 of 23 patients (9%) with remote (> 3 weeks) myocardial infarction. Only 2 of our 49 patients had congestive cardiomyopathy, but both had embolic events.

We conclude that in addition to the clinical setting, certain 2DE features of LVT may be associated with embolization. LVT that protrude into the left ventricular cavity or demonstrate FIM have a high incidence of embolic events. These data may be helpful when considering anticoagulation therapy.

DYNAMIC INTRACAVITARY ECHOCARDIOGRAPHIC PATTERNS ASSOCIATED WITH LEFT VENTRICULAR MURAL THROMBI: CLINICAL AND EXPERIMENTAL OBSERVATIONS

Frank L. Mikell, MD; Richard W. Asinger, MD; K. Joseph Elsperger, CCPT; W. Robert Anderson, MD; Morrison Hodges, MD. Hennepin County Medical Center and the University of Minnesota, Minneapolis, MN.

Of 49 patients (pts) with left ventricular mural thrombi (LVMT) detected by two-dimensional echocardiography (2DE), 6 had associated unusual dynamic echos within the left ventricle. Five of these 6 pts had left ventricular aneurysm (LVA). These dynamic echos had 2 patterns: one pattern (Type 1) was characterized by low amplitude swirling echos with a slow, circular motion in the region of the apex (3 pts). These echos were not attached to the LVMT. The other pattern (Type 2) consisted of highly mobile, tail-shaped echo masses which were attached to the LVMT but which were less acoustically intense (4 pts). One patient had both types.

Similar echo patterns were observed with 2DE in 7 of 9 dogs with experimentally induced LVA and LVMT. In the dogs, both patterns frequently occurred together. In dogs with the Type 1 swirling echos without the tail-shaped masses, only liquid blood was found in addition to the LVMT at autopsy. In dogs with the discrete tail-shaped masses, autopsy inspection showed well-formed, bright red masses which were attached to the LVMT. These red tails could be distinguished from the endocardial portion of the LVMT. Histologically these tails consisted mainly of red blood cells enmeshed in a fine fibrin network.

We hypothesize that both intracavitary echo patterns are associated with LVMT and represent early stages of the intravascular coagulation process. The Type 1 pattern may represent aggregates of blood elements or sluggish blood flow within the ventricle. In contrast, the tail-shaped echos represent well-formed thrombi which have different gross and histologic characteristics than the endocardial LVMT.

EFFECTS OF COUPLING INTERVALS ON CONTRACTION PATTERNS OF PREMATURE BEATS DERIVED BY COMPUTER ASSISTED TWO-DIMENSIONAL ECHOCARDIOGRAPHY

Takahisa Uchiyama, MD; Eliot Corday, MD, FACC; Samuel Meerbaum, PhD, FACC; Tzu-Wang Lang, MD, FACC; Pascal Gueret, MD, FACC; Thomas Peter, MD, Cedars-Sinai Medical Center, Los Angeles, California

Phasic alterations in LV segmental wall motion during arrhythmias were studied by computer assisted two-dimensional echocardiography (2DE). In a short-axis cross-section at the mid-papillary level, the ventricular wall and luminal area were displayed in 8 individual segments around a geometric center. LV wall motions were mapped during premature ventricular contractions (PVC) over a wide range of coupling intervals (CI) in 7 closed chest dogs. Areas were computed in end-diastole and end-systole (interobserver variability 2.8 to 9.3%) and a % systolic area change (SAC) was analyzed for the entire tomographic section and its 8 segments. With CI=80% of sinus rhythm, SAC was normal in all segments except near the pacing site. Successive reduction of CI to 40% led first to uniform lowering of PVC-SAC and eventually to sharply disrupted sequence and pattern of segmental contraction. Postextrasystolic potentiation was enhanced as CI decreased. Section SAC (%) data (mean±SD) were:

Mean CI	PVC Beat (N=24)	Potentiated Beat (N=24)
Long (62%)	31.9±8.5*	70.5±4.5*§
Short (39%)	8.2±4.8*	80.8±5.8*§

*p<.001 vs Sinus-SAC (60.0±6.3%) §p<.001 vs PVC

Conclusion: During premature contractions as coupling intervals were progressively reduced, 2DE portrayed increasing disruption of LV geometry and segmental dynamics. Shorter PVC coupling intervals were associated with greater postextrasystolic potentiation. Computer assisted 2DE is capable of providing a comprehensive quantitative analysis of cardiac function during arrhythmias.

WEDNESDAY, MARCH 18, 1981
PM
CORONARY CIRCULATION AND MYOCARDIAL BLOOD FLOW
2:00-3:30

ADRENERGIC TONE IN THE CANINE CORONARY CIRCULATION. Edward D. Verrier, MD, Gus J. Vlahakes, MD, Robert W. Baer, PhD, J. David Bristow, MD, FACC, Julien I.E. Hoffman, MD, FACC, FRCP. Cardiovasc. Res. Inst., U. of Calif., San Francisco.

Adrenergic tone may influence myocardial blood flow despite metabolic autoregulation. We examined this question in anesthetized dogs with a maximally vasodilated coronary circulation. Pressures were measured in the AO, LV, LA, and coronary sinus; heart rate was held constant by SA node block and atrial pacing (mean rate 115 min^{-1}). Diastolic coronary pressure-flow (P-Q) relations were determined with a circumflex preparation: coronary artery pressure was measured distal to a flow probe and occluder. Chromonar (8 $mg \cdot kg^{-1}$ iv) produced maximal coronary vasodilatation, confirmed by absence of reactive hyperemia. Twelve brief, partial occlusions were done at various distal pressures; mean diastolic coronary pressures and flows were used to construct a diastolic P-Q relation, which, with maximal vasodilatation, was linear [mean $r=0.98 \pm 0.01$ (SEM)]. P-Q lines were described by their slope and pressure intercept at zero flow. In 6 dogs, diastolic P-Q lines were determined before (Control) and after alpha blockade (AB) with phentolamine (5 mg iv). AO, LV, LA, and coronary sinus pressures did not change.

mean ± SEM	Control	AB	Analysis of variance
slope ($ml \cdot mm\ Hg \cdot min^{-1}$)	4.45 ± 0.51	4.37 ± 0.67	N.S.
intercept (mm Hg)	20.3 ± 0.4	17.9 ± 0.4	$P < 0.007$

AB produces a small, parallel, left shift in the P-Q line, which, with a large value for slope, increases diastolic coronary flow substantially at any given pressure during maximal vasodilatation. This suggests that alpha constrictor tone can limit myocardial blood flow despite maximal coronary vasodilatation and anesthesia.

In 4 other dogs, propranolol (0.25 $mg \cdot kg^{-1}$ iv) did not change either the slope or intercept of the diastolic P-Q line, suggesting that there is no significant resting beta tone in the canine coronary circulation under anesthesia.

BETA ADRENERGIC CONTROL OF LARGE CORONARY VESSELS IN CONSCIOUS DOGS

Pilar Macho, M.D. and Stephen F. Vatner, M.D., Dept. of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, Boston, MA 02115

While β adrenergic regulation of the coronary circulation has been studied extensively, an important aspect of this topic, i.e., β effects on large coronary vessels has not been examined in the intact animal. To study this, 8 dogs were instrumented with miniature, piezoelectric crystals on opposing surfaces of the left circumflex coronary artery, an electromagnetic flow probe on the same vessel and miniature pressure gauges in the aorta and left ventricle. One week after surgery isoproterenol, 0.1 μg/kg/min, in conscious dogs increased mean left circumflex internal coronary cross sectional area (CSA) by 17 ± 3%, decreased late diastolic coronary resistance (LDCR) by 42 ± 5%, while increasing heart rate by 66 ± 8% and left ventricular (LV) dP/dt by 58 ± 5%. Atenolol, 1 mg/kg, a β_1 adrenergic selective blocker, reduced CSA by 8 ± 1%, and increased LDCR by 12 ± 4% ($p<0.01$). After atenolol, isoproterenol with heart rate constant did not increase LV dP/dt and caused significantly less, $p<0.01$, increases in CSA (6 ± 1%) and decreases in LDCR (11 ± 2%). On a separate day, propranolol, 0.5 mg/kg, reduced CSA by 7 ± 1%, while LDCR rose by 13 ± 4%, $p<0.05$. Isoproterenol after propranolol induced no effect. Thus, β adrenergic stimulation causes substantial increases in large coronary vessel CSA. Surprisingly, the major fraction of this response was associated with β_1 mediated increases in LV dP/dt and heart rate, whereas β_2 dilation of these vessels played a much lesser role. Moreover, β blockade resulted in significant constriction of large coronary vessels, an effect which could be detrimental in the presence of coronary artery disease, where large coronary vessel CSA is of crucial importance.

EFFECTS OF PROSTACYCLIN (PGI_2) ON CORONARY BLOOD FLOW IN OPEN-CHEST DOGS AFTER DIFFERENT ROUTES OF ADMINISTRATION

Volker B.Fiedler, DVM,PhD; Depts.Pharmacology, Cassella, Frankfurt, F.R.G., and University of Michigan,Ann Arbor

Prostacyclin (PGI2) is a potent vasodilator in isolated perfused hearts of various species. The in-vivo effects of PGI2 infusions were investigated in anesthetized,open-chest dogs. Coronary flow (CBF) was measured with an electromagnetic flow probe around the left circumflex artery (LCX), and coronary vascular resistance (CR) was calculated while aortic pressure (AOP) and heart rate (HR)were recorded.

Intravenous infusion of PGI2 (0.05 to 1.0 μg/kg/min) reduced AOP and CR in a dose-dependent fashion but had only minor effects on CBF. A tachycardia occurred parallel to the pressure reduction. However, when administered intracoronary distal to the flow probe PGI2 increased CBF 3-4 fold (p at least <0.05) and reduced CR ($p<0.05$) without affecting AOP and HR in doses between 0.05 to 0.5 μg. Topical application of PGI2 on the right ventricle increased coronary sinus oxygen content with minor changes in pressure. Cyclo-oxygenase inhibition (indomethacin, 5 mg/kg/min i.v.) did not alter the hypotensive effects of PGI2 after i.v. administration and increased the coronary vasodilator potency of the compound.

The sensitivity of the coronary vasculature seemes to be enhanced to PGI2 when endogenous biosynthesis of prostaglandin-like substanses is inhibited. Only after direct administration of PGI2 into the coronary circulation its specific coronary vasodilating effects can be demonstrated thus excluding the metabolization in the lung after intravenous application. It is suggested that PGI2 might be involved into the regulation of the coronary ciculation and coronary blood flow changes.

INFLUENCE OF NIFEDIPINE ON MYOCARDIAL BLOOD FLOW DURING THREE GRADES OF CORONARY OCCLUSION

William S. Weintraub, MD; Shigehiko Hattori, MD; Jai B. Agarwal, MD; Monty M. Bodenheimer, MD, FACC; Vidya S. Banka, MD, FACC; Richard H. Helfant, MD, FACC, Presbyterian-University of Pennsylvania Medical Center, Phila., Pa.

The effect of nifedipine (Nif) on myocardial blood flow (MBF) at varying grades of partial coronary occlusion (PO) is unknown. Thus 22 open chest dogs underwent carotid to left anterior descending perfusion with flow and perfusion pressure monitoring. Grades of coronary occlusion were defined by minimum diastolic perfusion pressure (DPP). After DPP was reduced to 54 mmHg (6 dogs), 37 mmHg (10 dogs) or 24 mmHg (6 dogs) 10 ug Nif was given intracoronary. Regional MBF in ml/g/min was determined by tracer microspheres. The three partial occlusions showed differing increases in total flow (%CF) and regional flow.

	Ischemic Zone MBF				Normal Zone MBF				
DPP	Endo		Epi		Endo		Epi		%CF
mmHg	PO	Nif	PO	Nif	PO	Nif	PO	Nif	
54	1.06	1.14	1.15	1.96*	1.29	1.28	1.11	1.10	42.3
37+	.70	.60*	1.06	1.39*	1.28	1.28	1.16	1.15	18.6+
24+	.48	.48	1.01	.94	1.54	1.49	1.60	1.57	-8.3+

*compared to control, +compared to above $p<.01$

At 54 mmHg Nif caused an increase in Epi MBF but no change in Endo MBF. In contrast at 37 mmHg Nif caused Epi flow to increase but resulted in a decrease in Endo flow. At the lowest perfusion pressure (24 mmHg) Nif caused no change in zone MBF. Thus the severity of coronary stenosis determines the presence of coronary vascular reserve in the endo and epicardium and thus the effect of nifedipine on regional myocardial perfusion. In certain settings, vasodilators such as nifedipine cause a redistribution or steal of flow from endocardium to epicardium.

LIMITED INFLUENCE OF CAPACITIVE EFFECTS ON CORONARY PRESSURE-FLOW RELATIONS AND ZERO-FLOW PRESSURES DETERMINED DURING SINGLE LONG DIASTOLES

James F. Klocke; David R. Kraus, BS; Irwin R. Weinstein, MD; Robert E. Mates, PhD; Francis J. Klocke, MD, FACC, State University of New York at Buffalo, New York

Bellamy's analysis of coronary pressure-flow relations during long diastoles indicates that coronary inflow normally ceases at a pressure >20 mm Hg. Eng and Kirk have suggested that measurements of epicardial inflow importantly underestimate capillary flow during long diastoles because of capacitive discharge of blood from precapillary vessels as inflow pressure falls. Accordingly, the left circumflex artery (LC) was cannulated in open-chest heart-blocked dogs and, using paired solenoids, perfused from either the aorta or a constant-pressure blood reservoir. The pressure-flow relation defined from single post-pacing diastoles during aortic perfusion was compared to the similar relation defined by points obtained by switching from aortic to reservoir perfusion at the onset of diastole over a wide range of reservoir pressures. Both relations were concave to the flow axis at lower LC pressures, and better fit by second-order than first-order equations. In eight animals with systolic pressures of 100-130 mm Hg, values for the curvilinear pressure-axis intercept ($P_{f=0}$) averaged 27 ± 5 (SD) mm Hg for variable-pressure aortic perfusion and 23 ± 4 mm Hg for constant-pressure reservoir perfusion ($p < 0.01$); differences in individual animals ranged from 3 to 7 mm Hg. Differences were smaller in similar studies during maximum vasodilation, $P_{f=0}$ being 12-15 mm Hg with both aortic and reservoir perfusion (but still higher than intracavitary diastolic pressures). Thus, the magnitude of capacitive discharge of blood during a long diastole appears insufficient to explain the differences between $P_{f=0}$ and RA and/or LV diastolic pressures now reported by several laboratories.

HOW DOES SYSTOLIC CORONARY ARTERY COMPRESSION CAUSE MYOCARDIAL ISCHEMIA IN DOGS?

Jacques R. Rouleau, MD, FACC; Jean-G. Dumesnil, MD; Louis Roy, MD; Gilles-R. Dagenais, MD, FACC, Quebec Heart Institute, Quebec, Canada.

The mechanism by which muscular coronary artery (CA) overbridging can cause ischemia is unclear since LV subendocardial blood flow is diastolic and CA compression systolic. To evaluate such a mechanism, we studied systolic compression (SC) of the proximal left circumflex CA in 10 anesthetized dogs both with autoregulation (A) and during maximal CA vasodilatation (V). Mechanical SC, triggered by ECG signal via a solenoid, was adjusted to interrupt CA flow only during the aortic ejection period. During control state and SC, we measured LV, AO and distal circumflex CA pressure (CP), phasic coronary blood flow proximal to SC, regional myocardial blood flow (RMBF) using 15 um diameter spheres, myocardial oxygen consumption (MVO_2) and myocardial lactate extraction (MLE). With SC, during A and V, there was a similar diastolic time lag to restart phasic CA blood flow (34±3 vs 31±3 msec) and to increase CP (69±4 vs 79±6 msec). With A, SC reduced the diastolic coronary:systolic LV pressure time ratio (DPTIc:SPTI)(1.09±0.10 vs $0.79\pm0.10^{+}$) and, due to effective A, RMBF was unchanged (101±10 vs 96±9 ml/min/100 g) as were the other measured variables. During V, SC decreased the circumflex vasodilatory reserve by 47% (439±61 vs 234±34 ml/min/100 g^{+}), the DPTIc:SPTI ratio (0.72±0.09 vs $0.55\pm0.07^{+}$), MVO_2 (14.2±2.2 vs 11.6±2.1 ml/min*) and MLE became negative; the inner:outer RMBF distribution was linearly related to the pressure ratio DPTIc:SPTI (r:80), independent of SC. Thus with maximal V and increased heart rate the diastolic time lag necessary to reopen the CA bed during SC becomes a limiting factor to myocardial perfusion. ($^{+}p<0.005$; $*p<0.05$)

WEDNESDAY, MARCH 18, 1981
PM
NUCLEAR CARDIOLOGY: CLINICAL APPLICATIONS
2:00-3:30

VALUE OF MEASURING ANAEROBIC THRESHOLD DURING RADIONUCLIDE EXERCISE TESTING IN AORTIC REGURGITATION

Charles A. Boucher, M.D., FACC, David J. Kanarek, M.D., Harry R. Phillips, M.D., Richard R. Liberthson, M.D., Robert D. Okada, M.D., FACC, Peter C. Block, M.D., FACC, H. William Strauss, M.D., FACC, Gerald M. Pohost, M.D., FACC. Massachusetts General Hospital, Boston, MA.

The change (Δ) in ejection fraction (EF) from rest to peak exercise (ex) is being used to assess LV reserve in severe aortic regurgitation (AR). However, peak ex also reflects such factors as fitness and motivation. To standardize the approach to ex and to better understand the EF response, 11 catheterized normal and 26 AR patients with minimal or no symptoms underwent graded supine ex gated blood pool scans to peak tolerance. Oxygen uptake and ventilation were measured along with EF at each 3 min ex level. Anaerobic threshold (AT), which defines the earliest functional limitation during ex, was the ex level at which ventilation/oxygen uptake increased due to lactic acid production. EF at rest, AT and peak ex and the ΔEF before and after AT were compared. AR patients were divided based on the 2SD lower limit of ex capacity in normals: Group A with peak oxygen uptake >13 (17 patients) and Group B <13 ml/kg/min (9 patients). Mean ±1 SD values follow: (*p<.01)

Group	Rest EF	(ΔEF)	EF at AT	(ΔEF)	Peak EF
Normal	67±6%	(+6±6)*	73±5%*	(0±10)	73±10%*
A (AR)	62±7%*	(-1±4)*	61±10%*	(-5±5)	56±14%*
B (AR)	47±15%*	(-9±5)	38±13%	(-5±3)	33±13%

In AR, ΔEF with ex has 2 components based on AT. The first, ΔEF before AT, is related to functional reserve, whereas the second, ΔEF after AT, falls in all patients and is unrelated to functional reserve. These data suggest that ΔEF before AT provides adequate diagnostic information. Since AT is a submaximal and physiologic endpoint, ex beyond AT to peak tolerance is unnecessary.

RADIONUCLIDE ANGIOCARDIOGRAPHIC ASSESSMENT OF PATIENTS FOLLOWING REPAIR OF TRANSPOSITION OF THE GREAT ARTERIES

Roger A. Hurwitz, MD, FACC; Nicholas Papanicolaou, MD; Salvador Treves, MD; John F. Keane, MD; Aldo Castaneda, MD, FACC, Children's Hospital Medical Center, Boston, MA.

The utility of radionuclide angiocardiography (RAC) to detect the presence and progression of vena cava obstruction or residual left-to-right shunt was evaluated in patients 6 days to 3 years following surgical repair of transposition of the great arteries (TGA). Results of first pass RAC were compared to data obtained during cardiac catheterization (CC). Totally, 24/25 patients had good correlation between RAC and CC. Among 20 patients with clinical evidence of vena cava obstruction, early post-operative RAC and concurrent or subsequent CC excluded obstruction in 10. Significant obstruction was identified in 9 by both RAC and CC. In the remaining patient, obstruction was absent early post-operatively when evaluated by RAC, but was present 2 years later at CC. Among 5 patients with serial RAC and CC, satisfactory correlation was evident with either continued vena cava patency or progressive obstruction. All 5 patients with significant shunt (Qp:Qs > 1.5) measured at CC had almost identical flow ratios estimated by RAC. In another 4 patients, a questionable shunt at early post-operative RAC was absent at later CC. We conclude that following TGA repair, RAC is a valuable non-invasive method to identify (a) vena cava patency or obstruction, (b) progression of vena cava obstruction, and (c) significant residual shunts.

SERIAL RADIONUCLIDE ASSESSMENT OF DOXORUBICIN CARDIOTOXICITY IN CANCER PATIENTS WITH ABNORMAL BASELINE RESTING LEFT VENTRICULAR PERFORMANCE

William Choi, MD; Harvey Berger, MD; Jon Alexander, MD, FACC; Peter Schwartz, MD; Frans Wackers, MD, FACC; Barry Jaret, MD, FACC, Yale University School of Medicine and Yanbury Hospital; New Haven, Ct.

Previous studies from this laboratory have established guidelines for safe administration of doxorubicin to cancer patients (pts) with normal (nl) left ventricular (LV) performance. Over 36 months (mos), 48/329 pts (15%) referred for first-pass radionuclide evaluation of LV function had abnl (<55%) baseline resting LV ejection fraction (EF) prior to receiving doxorubicin. Thirty-one/48 pts had no evidence of antecedent heart disease. Sixteen/48 pts had received prior thoracic radiation therapy. Serial LVEF measurements were obtained over 2-15 mos of therapy in 29 pts. Of 18 pts not studied serially, 9 were denied doxorubicin because of abnl LVEF.

Initial LVEF averaged (±SD) 48±5% (range, 30-54%) in the 29 pts followed serially. After receiving 313±144 mg/M^2 (120-600 mg/M^2) of doxorubicin, final LVEF was unchanged (47±9%, pNS). In the 12 pts who received ≥350 mg/M^2, there also was no difference between initial and final values (48±8 vs 43±4%, pNS). LVEF declined by ≥10% in only 4 pts (12-18% EF units). One of these pts developed congestive heart failure (CHF) at 460 mg/M^2. No other pt developed CHF during therapy or long-term follow-up. Eleven/48 pts are still receiving doxorubicin in spite of abnl LVEF; the remaining 14 pts are either in remission or have died due to progression of disease.

Thus, abnl LV function is present in a substantial number of cancer pts without clinically evident antecedent heart disease. Doxorubicin can be administered safely in the presence of abnl baseline LV function using serial radionuclide studies as a means of monitoring therapy.

INDIUM-111 PLATELET SCINTIGRAPHY AND TWO DIMENSIONAL ECHOCARDIOGRAPHY IN THE DIAGNOSIS OF LEFT VENTRICULAR THROMBI

Michael D.Ezekowitz,MD,FACC; Don A.Wilson,MD; Eileen O. Smith,BS; Paul J.Kanaly,MD; Don E.Parker,PhD, University of Oklahoma Health Sciences Center, Oklahoma City, Okla.

The purpose of this study was to define the relative roles of these techniques in the diagnosis of mural thrombi (T) in patients (P) in whom the diagnosis could be surgically verified. Two groups of P were studied. Group I (n=19) consisted of P undergoing coronary artery bypass surgery with aneurysmectomy. Group II (n=8) were P undergoing mitral valve replacement and had non-significant coronary disease. All P had 2 dimensional echocardiograms (2DE); 18/19 in Group I and 8/8 in Group II had platelet scintigraphy (PS). Two DE images were obtained in parasternal long and short axis views and apical four chamber views and analyzed in real time, slow motion and stop action modes by 2 blinded observers. Each study was analyzed according to technical quality (excellent, adequate, poor) and probability of thrombus (positive, negative and possible). PS were analyzed by 2 observers in the LAO, RAO, L lateral and anterior views after injection of Indium-111 platelet suspension. Both observers graded 7/27 echos as excellent, 17/27 as adequate and 3/27 as poor; the latter category was not analyzed further. In Group I, 2DE had a sensitivity of 90% (both observers) and a specificity of 50% and 67% (observer 1 and 2). Both readers recorded 2 possibles which were negative at surgery. Observer agreement was 16/19 (84%). The sensitivity and specificity of PS was 80% and 100% (both observers). In Group II, all studies were true negatives by both techniques. It is concluded that: 1) 2DE appears more sensitive but less specific than PS. 2) 2DE identifies mass lesions while PS reflects 'haematological activity'. 3) The two techniques compliment each other.

DETECTION OF LEFT VENTRICULAR THROMBI BY RADIONUCLIDE ANGIOGRAPHY.

J.R. Stratton, M.D., J.L. Ritchie, M.D., K.E. Hammermeister, M.D., J.W. Kennedy, M.D., G.W. Hamilton, M.D. U. of Washington, Seattle, WA.

Filling defects compatible with left ventricular thrombi are occasionally noted on equilibrium radionuclide angiograms. To define the usefulness of this finding for the detection of LV thrombi, we blindly interpreted the anterior and left anterior oblique cineangiograms of 39 pts who had either proof of absence of thrombus (26 pts) by autopsy (24) or cardiac operation (2) or proof of presence of thrombus (13 pts) by autopsy (5), operation (2), or Indium-111 platelet imaging (6). Five pts with positive platelet imaging also had positive 2D echos for thrombus; the sixth pt did not have echo.

Overall, 13 angiograms were positive (10) or equivocally positive (3) for thrombus, and 26 were negative. Three studies were falsely positive and three falsely negative. Sensitivity of radionuclide angiography for detection of thrombus was 77% and specificity was 88%. All thrombi detected appeared on the anterior view as either a discrete apical filling defect (8 pts) or as a squared LV apex (2 pts). Two of 3 falsely positive studies had only LAO defects without anterior defects. Thirteen pts (8 with thrombus, 5 without) had 2D echos which were blindly and independently interpreted. Echo was 100% sensitive and specific in this small group. Risk factors for presence of thrombus included transmural anterior MI, LV aneurysm, and low ejection fraction. All 13 pts with thrombi had anterior MI vs. 7/26 (27%) of pts without thrombi ($p<.01$). Nine of 13 pts (69%) with thrombi had aneurysms vs. 7/26 (27%) of pts without thrombi ($p = .02$). Mean ejection fraction in pts with thrombi was .29 vs. .41 in pts without thrombi ($p = .05$). Six of 13 pts (46%) with thrombi had systemic emboli vs. 1/26 (4%) of pts without thrombi ($p < .01$).

The finding of a discrete filling defect or squared LV apex on radionuclide angiography is a useful clue to the presence of a LV thrombus, which can be confirmed by other noninvasive studies.

RADIONUCLIDE VENTRICULOGRAPHY FOLLOWING RESUSCITATION FROM OUT-OF-HOSPITAL VENTRICULAR FIBRILLATION

Gene B. Trobaugh, MD; Brian W. Gross, MD; Jeffrey A. Werner, MD, FACC; H. Leon Greene, MD, FACC; Gary Caputo, MD; Glen W. Hamilton, MD, FACC; Leonard A. Cobb, MD, FACC, Harborview Medical Center, Seattle, Wa.

Thirty-four patients (pts) who survived initial resuscitation from out-of-hospital ventricular fibrillation (VF) without isoenzyme evidence for necrosis had a radionuclide ventriculogram (RNV) within 12 hours after VF. Studies were repeated 1 week later in 24 pts. The left ventricular wall motion was visually assessed by independent two observers.

On admission, the mean LVEF was 36%± 18% (±1S.D.) and ranged from 8% to 71%. The most abnormal of the six wall segments was normal or slightly hypokinetic in 7 (21%), moderately hypokinetic in 2 (6%), severely hypokinetic in 10 (29%), akinetic in 5 (15%) and dyskinetic in 10 (29%). The average number of wall segments which manifested severe hypokinesis, akinesis, or akinesis was 2.4 ± 2.1.

The admission LVEF was lower in those who died (n=10) during hospitalization than those lived to be discharged (n=24) (29%± 19% vs. 39%±17%, p=.05). Those who died also had more segments with severe hypokinesis (or worse) contractility (3.5± 2.0 vs. 1.9±2.0, p<.001).

In the 24 pts who also had a RNV performed a week later, the LVEF increased by 16%±12% ($p< .001$) and the average number of wall segments with severe hypokinesis (or worse) decreased by 1.9 ± 1.4 ($p < .001$).

Following out-of-hospital VF in those without necrosis, there is an overall increase in LVEF and improved contractility during the first week of hospitalization in those who lived to be discharged. The admission LVEF was significantly lower and contractility was worse in those who died.

WEDNESDAY, MARCH 18, 1981
PM
THE VENTRICLES III: MEMBRANE ACTION POTENTIAL STUDIES
4:00-5:00

EFFECT OF ISOPROTERENOL ON "RESIDUAL FAST CHANNEL-DEPENDENT SLOW CONDUCTION" PRODUCED IN GUINEA PIG VENTRICULAR MUSCLE

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We studied the effect of isoproterenol (ISP) on upstroke and duration of action potentials (AP's) and conduction velocity in incompletely depolarized ventricular papillary muscle whose resting potential was -57 ± 2 mV in high K^+ (14 mM)-Tyrode solution with microelectrodes. Without ISP, the AP upstroke had a slur and the maximum rate of rise ($\dot{V}$ max) was made of 2 components: the first large (13 - 27 V/s) and the second small (less than 8 V/s) ones (split $\dot{V}$ max). The conduction velocity was less than about 30 cm/s ("slow conduction"). The first $\dot{V}$ max was depressed by TTX (10^{-6} M) and the second, by l-verapamil (1 µg/ml) indicating that the impulses were transmitted via the first one, i.e., "residual fast channel". The recovery of excitability measured using $\dot{V}$ max of premature AP's with basic rate of 0.1 Hz revealed a rapid (τ= 40.6 ± 3.5 ms) followed by a slow (τ= 533.3 ± 48.3 ms) recovery process. No rate-dependent change in AP duration and refractory period was found among rates 0.1, 0.5 and 0.9 Hz tested. ISP (5 x 10^{-7} M) selectively increased and approximately quadrupled the second component of the split $\dot{V}$ max overcoming the first. ISP produced marked rate-dependent shortening of AP duration, being maximum at 0.1 Hz (226 ± 17 ms) and minimum at 0.9 Hz (149 ± 16 ms) with significant shortening of post repolarization refractoriness, but produced no change in recovery kinetics of $\dot{V}$ max. The results suggest that "residual fast channel" could produce "slow conduction" without ISP and that main ionic channels (fast and slow) responsible for some slow conduction in reentry may alternate according to local concentration of tissue catecholamines.

STABILIZING EFFECT OF INSULIN ON AUTOMATICITY IN PARTIALLY DEPOLARIZED CARDIAC PURKINJE FIBERS

Joseph Reiser, Ph.D., Gary J. Anderson, MD., FACC, John Swartz.Hahnemann Medical College & Hospital,William Likoff Cardiovascular Institute, Philadelphia, Pennsylvania

The purpose of this study was to evaluate the effect of insulin (I) on automaticity (Au) and membrane potential (MP) of cardiac Purkinje fibers showing low MPs.Existing depressed fibers and stretched-induced depolarized tissue was studied utilizing standard microelectrode techniques. In 8 experiments,I (.048 µ/cc) induced the following electrophysiologic effects after 40 min exposure:

Control	MDP(mV)	APA(mV)	(IR(b/min)	dE/dt(mV/s)
(Mean±SE)	68.56	50.65	41.51	12.63
	±4.3	±7.9	±6.7	±2.1
Insulin				
(Mean±SE)	87.7	85.4	24.5	6.6
	±1.9	±6.1	±5.1	±1.0
P	<.01	<.01	<.01	<.01

MDP-Maximum Diastolic Potential,APA-Action Potential Amplitude, IR-Intrinsic Rate,dE/dt-ph 4 slope.
In contrast, spontaneous fibers showing normal MPs showed insignificant effects after a similar time period of I exposure.I given before or after epinephrine (10^{-7}-5 x 10^{-6}M) did not affect the rate of epinephrine-induced Au or the MP (n=7,p=NS).These results suggests that I exerts a direct effect on the cell membrane which is primarily manifest as an increase in the MP. The stabilizing effect on Au is related to improved MP. Since this effect does not occur in fully polarized cells,these data suggest that either Na,K pump activity or membrane conductance is impaired in depolarized cells.This concept is supported by the failure of I to effect normal cells or cells exposed to epinephrine, where pump activity and potassium conductance are optimized.Thus,I through its stabilizing effect on the cell membrane may be antiarrhythmic.

SITE OF ACTION OF LOCAL ANESTHETICS ON HEART FIBERS

Lawrence H. Frame, MD., Gary A. Gintant and Brian F. Hoffman, MD, FACC. Columbia University, New York, N.Y.

For nerve and muscle there is evidence that the charged form of lidocaine interacts during stimulation with the fast inward channel from the inner surface of the membrane and that a period of quiescence causes partial recovery from block of I_{Na}. We have used QX-314 (QX) ((N-(2,6-dimethylphenyl)-carbamoylmethyl)triethylammonium bromide), a quaternary derivative of lidocaine, to evaluate this question for canine Purkinje fibers (PF). Block of fast channels was quantified by measuring $\dot{V}$max of phase 0 of the action potential (AP) recorded using intracellular microelectrodes. Superfusion with Tyrode solution (K^+=2.7 or 4.0mM) containing QX (1-4x10^{-3}M) slowly decreased $\dot{V}$max of the stimulated AP (cycle length = 1 sec) by 30-60%. After quiescence, the $\dot{V}$max of the first AP equaled the drug free value of $\dot{V}$max. The $\dot{V}$max of subsequent AP's during regular stimulation rapidly decreased to the reduced value recorded prior to quiescence. All of these phenomena persisted after returning to superfusion with drug free Tyrode solution. In separate experiments intracellular injection of QX during superfusion with drug free Tyrode solution produced a rapid reduction of $\dot{V}$max to 30-60% of control at the site of injection. After 2-5 minutes of quiescence the $\dot{V}$max of the first AP approached the control value and then again decreased during stimulation to the same level that preceeded quiescence. This recovery of $\dot{V}$max during quiescence probably is due to dissociation of QX from fast channels. The subsequent decrease to the same depressed value of $\dot{V}$max that preceeded quiescence suggests that the dissociated QX was confined intracellularly. These findings indicate that QX interacts with fast channels from the inner surface of the sarcolemma and also that PF are permeable to charged local anesthetic molecules.

NIFEDIPINE BUT NOT VERAPAMIL HAS AGE-INDEPENDENT EFFECTS ON CARDIAC REPOLARIZATION.

Alan M. Ezrin, Ph.D., Agustin Ramos, M.D., Angel Leon, B.S., Arthur L. Bassett, Ph.D., Henry Gelband, M.D., FACC. Univ. of Miami, Miami, Fla.

The Ca^{2+}-antagonists verapamil and nifedipine reportedly affect myocardial repolarization (Q-T interval) differently. This study delineates the cellular mechanism underlying the effects of these drugs on Purkinje fiber (PF) repolarization in adult and neonatal hearts. Activation of K^+-repolarizing channels in adult PF is modulated by Ca_i^{2+} (Isenberg, G. Pflug. Arch. 371:61-69, 1977), and is delayed by exposure to verapamil or low Ca_o^{2+}. However, repolarization of neonatal PF is not delayed by verapamil or low Ca_o^{2+}. This suggests that changes in Ca_i^{2+} do not influence K^+-repolarizing channels in the immature heart. Newborn (1-9 days) and adult rabbit PF were isolated and action potentials (AP) were monitored using standard microelectrode techniques (36° C; BCL = 630 msec). Phase 2 duration (AP plateau) in both age groups was shortened by verapamil (2 µM) or nifedipine (0.1 - 2 µM), whereas their effects upon repolarization differed. Verapamil increased AP duration (APD_{90}), effective refractory period (ERP) and prolonged phase 3 (terminal repolarization) in adult PF. Nifedipine decreased APD_{90} and ERP, while phase 3 was unaffected. In contrast, both drugs decreased phase 2 duration, APD_{90} and ERP in neonatal PF. Verapamil (2 µM) and nifedipine (0.1 - 2 µM) abolished high K^+ (20 mM) induced slow responses generated by adult and neonatal PF. Our data demonstrate an age-independent effect of nifedipine upon repolarization. We suggest that nifedipine shortens APD in adult PF by decreasing the inward Ca^{2+} current. In contrast to verapamil, attenuation of the slow inward current by nifedipine is unrelated to Ca_i^{2+} control of K^+ repolarizing channels in adult hearts.

WEDNESDAY, MARCH 18, 1981
PM
PACING AND TACHYCARDIA
1:00-5:00

TWO YEARS' CLINICAL EXPERIENCE WITH A SELF-SEARCHING TACHYCARDIA PACEMAKER

Edgar Sowton, MD, FRCP, FACC; Håkan Elmqvist, Christer Hård af Segerstad, Guy's Hospital, London, England.

5 patients with reciprocating tachycardia have been treated with a pacemaker which automatically identifies the correct timing to terminate attacks with ectopic beats. This is done by successive approximation with earlier or later adjustment of the timing by a microprocessor according to the electrophysiological response to the last stimulus. Timing steps become progressively smaller allowing stimulation even in extremely narrow windows of a few milliseconds duration. Double stimuli are automatically delivered if 6 attempts with single stimuli fail to terminate tachycardia, and successful timing is remembered for the first stimulus during the next episode of tachycardia.

5 patients have been treated over 2 years with one version of this apparatus which activates an implanted stimulator via skin impulses. 4 patients have WPW, 3 AV nodal tachycardia and 1 VT. Attacks occurred up to 10 times a day and have all been terminated by critically timed stimuli. In most patients the left-hand edge of the termination window is constant within 10 mseconds and attacks are then terminated by the first or second stimulus; standing up or exercise contracts the window usually by advancing its right-hand (late) limit. The pacemaker has identified these changes, as well as those produced by beta blockers, disopyramide, quinidine or verapamil and has terminated tachycardias with most episodes requiring less than 3 steps.

AUTOMATIC CYCLE LENGTH ADJUSTMENT-A VERSATILE PACEMAKER FOR TACHYCARDIA TERMINATION

Anthony Nathan,MB;Kevin Hellestrand,MB;John Camm,MB; Goworth Spurrell,MD,FACC.
St.Bartholomew's Hospital,London,England.

When overdrive pacemakers(PM) fail to terminate tachycardia(T), frequent futile repititions of the same pacing sequence usually occur. A new PM is described in which failure to terminate T leads to a reduction in pacing cycle length by 6 msec before termination is reattempted, a process that may be repeated upto a maximum of 16 times. This PM is capable of delivering a preset number of stimuli(1 to 15) in response to a T defined as 4 successive beats occuring at a rate faster than a preset value. The initial coupling interval and subsequent pacing cycle intervals are always equal.After successful conversion a further episode of T evokes the previously successful pacing sequence.A bradycardia standby function is incorporated.

The system was evaluated in 15 consecutive patients with recurrent supraventricular T(11 atrioventricular,4 intranodal) during electrophysiological study. T cycle length ranged from 245-450(mean 363)msec.Right ventricular bipolar pacing was successful in all patients.1 stimulus terminated T in 5 patients, 2 stimuli were effective in a further 8, and 2 required 5 and 6 stimuli.No unwanted arrhythmias were induced.

This PM has proved clinically valuable for the repeated termination of recurrent spontaneous T, as well as for T induced at electrophysiological study.The non-competitive nature of this mode of pacing reduces the likelihood of provoking unwanted arrhythmias, but the theoretical risks associated with rapid bursts of ventricular pacing require further evaluation.

BENEFITS AND RISKS OF COMBINED BURST PACING AND DRUG THERAPY OF RECURRENT VENTRICULAR TACHYCARDIA.

H.J. Duff, M.D., S. Reele, M.D., D.M. Roden, M.D., E.L. Carey, M.D., J.W. Hammon, M.D., R.L. Woosley, M.D.,Ph.D. and R.F. Smith, M.D., FACC. Departments of Pharmacology and Medicine, Vanderbilt University School of Medicine, Nashville, TN.

As a possible aid in the management of recurrent sustained ventricular tachycardia (VT), a radio frequency-energized and manually-controlled Medtronic 5998 pacemaker (VP) with a transvenous ventricular electrode was implanted in 6 patients (pts) whose VT was partially controlled by drugs and who required repeated cardioversions. The effectiveness of asynchronous bursts of rapid ventricular pacing was established in all pts prior to VP implantation. Drug therapy was continued in 5/6 pts after VP implantation. The 6 pts have been followed for a mean of 9 months (range 1-18 mo.). One pt, an alcoholic who refused additional therapy, died suddenly. Surviving pts have continued to require conversion by VP; recurrence rates range from 1/yr. - 48/yr. In each case, the pt was instructed to report to a hospital when VT occurs and was carefully monitored when conversion was done. VP has been successful in all episodes but adjustments in VP rate were required in 3/6 pts. The rate adjustment of the Medtronic 5998 unit is not accurately calibrated and on 2 occasions, VP was inadvertently set at greater than 300 BPM causing ventricular fibrillation in 1 pt. The rate of the VP unit can be checked externally by counting audible clicks on an AM radio placed next to the radio frequency unit. Conclusion: VP provides an alternative method of terminating VT and when used with drug therapy, aids in pt. management. Rate adjustments are frequently necessary and excessive ventricular rates may cause ventricular fibrillation. Therefore, pts should be monitored during conversions and a defibrillator should be readily available.

LONG-TERM EFFECTIVENESS OF DUAL-DEMAND SEQUENTIAL PACING FOR AUTOMATIC CONVERSION AND PREVENTION OF REFRACTORY REENTRY SUPRAVENTRICULAR TACHYCARDIA

James D. Maloney, MD, FACC; Victor Medina-Ravell, MD; Otto Hernandez Pieretti, MD; Bohvar Portillo, MD; Castor Maduro, MD; Barouh Berkovits, FACC; Federico Moleiro, MD, Mayo Clinic, Rochester, Minnesota, and Universidades Central and Zulia of Venezuela, Valencia, Venezuela

Eight patients (pts) with refractory symptomatic paroxysmal supraventricular tachycardia (PSVT) received dual-demand atrioventricular sequential pacemakers--5992DD--(DDS) for control and automatic underdrive conversion of PSVT. All had recurrent syncope and were symptomatic for 6 to 40 years. Paroxysmal atrial fibrillation (PAF) with antegrade conduction occurred in 3. Ventricular fibrillation was observed in 1.

Pre- and post-DDS assessment included Holter monitoring and regular follow-up visits. His bundle studies with programmed electrical stimulation documented PSVT mechanism and effectiveness of DDS underdrive conversion in acute settings. PSVT mechanism included 3 pts with WPW-A, 1 patient with WPW-septal, 2 pts with WPW-B, and 2 pts with AV nodal reentrance.

Follow-up observations for 6 to 20 months demonstrated continuing effectiveness of DDS in recognizing and converting spontaneous PSVT. In 2 pts, PSVT has been totally prevented and the frequency and duration of PSVT markedly reduced in 4. Concurrent drugs were reduced or eliminated in all. Pacemaker complications have not been observed.

Chronic effectiveness of DDS for prevention and conversion of PSVT in selected pts is demonstrated. PAF is not a contraindication.

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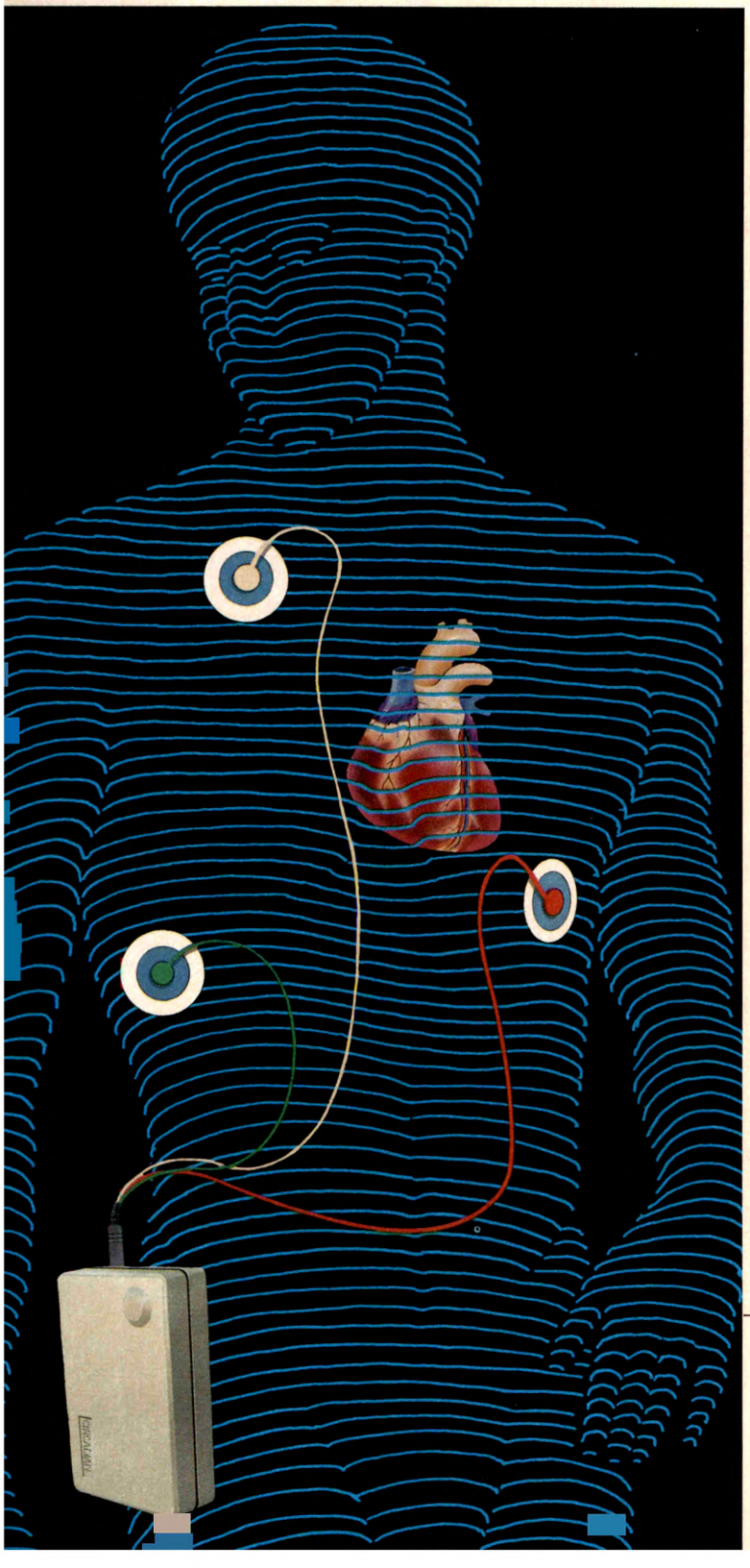

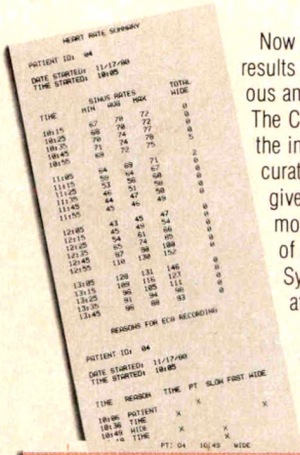

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Consider the anginal heart at stress: It works harder, faster. Needs more oxygen. Pumps harder, faster still. Strives for more oxygen—with pain. Anginal attack means more nitroglycerin. And that means faster heart rate. The cycle repeats.

Consider Inderal: It reduces heart rate—therapeutically—by some 12 beats a minute.[1-6] 720 fewer beats per hour. Some 6 million fewer beats per year. That means less work for the anginal heart. Less oxygen demand by the myocardium. Fewer anginal attacks. Less need for sublingual nitroglycerin. More tolerance for exercise—and more freedom of action.

Reduction in heart rate is modest: should not be cause for concern.[7] The relatively low dosages required for angina prophylaxis (an average of 160 mg/day) produce few, if any, serious adverse reactions, which in any case are readily recognized and controlled.

With proper patient selection—in the absence of bronchial asthma, sinus bradycardia, or heart block greater than first degree—risk of precipitating cardiac failure is extremely rare. And withdrawal problems may be avoided by reducing dosage gradually—rather than abruptly.*

Consider too: There is also a favorable redistribution of perfusion to the vulnerable subendocardium.[8] And, in patients who may still need nitroglycerin p.r.n., INDERAL will cancel the undesirable increase in heart rate and contractility.

Prescribe INDERAL with confidence. Effective. Reliable. For patients with moderate to severe angina in whom conventional measures have failed.

For full information on Contraindications, Precautions, Adverse Reactions, and Warnings, including avoidance of abrupt withdrawal, please consult the prescribing information on the following page.

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BRIEF SUMMARY
(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)
Inderal® BRAND OF
PROPRANOLOL HYDROCHLORIDE
A beta-adrenergic blocking agent

BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

ACTIONS

Beta receptor blockade is useful in conditions in which, because of pathologic or functional changes, sympathetic activity is excessive or inappropriate and detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

The proper objective of beta blockade therapy is to decrease adverse sympathetic stimulation but not to the degree that may impair necessary sympathetic support.

Propranolol may reduce the oxygen requirement of the heart at any given level of effort by blocking catecholamine-induced increases in heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. On the other hand, propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure, and systolic ejection period.

If the net physiologic effect of beta adrenergic blockade in angina is advantageous, it would be expected to manifest itself during exercise by delayed onset of pain due to decreased oxygen requirement.

INDICATION

Angina Pectoris Due to Coronary Atherosclerosis: The initial treatment of angina pectoris involves weight control, rest, cessation of smoking, use of sublingual nitroglycerin, and avoidance of precipitating circumstances. INDERAL is indicated in selected patients with moderate to severe angina pectoris who have not responded to these conventional measures. Propranolol should not be used in patients with angina which occurs only with considerable effort or with infrequent precipitating factors.

INDERAL exerts both favorable and unfavorable effects, the preponderance of which may be beneficial. (See ACTIONS Section.) INDERAL should not be continued unless there is reduced pain or increased work capacity.

Because of the potential for adverse results, treatment should be carefully monitored. The patient should also be reevaluated periodically since the dosage requirement and the need to continue INDERAL may be altered by clinical exacerbations or remissions. (See DOSAGE AND ADMINISTRATION.)

Additional studies of the effects of INDERAL in angina pectoris patients are in progress to better evaluate and define the proper role of INDERAL in this condition.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONC EMPHYSEMA), INDERAL should be administered with caution since it may block bronch tion produced by endogenous and exogenous catecholamine stimulation of beta recept

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adre blocking activity, INDERAL may prevent the appearance of premonitory signs and symp (pulse rate and pressure changes) of acute hypoglycemia. This is especially important t in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by cipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been es tablished. Use of any drug in pregnancy or women of childbearing potential requires tha possible risk to mother and/or fetus be weighed against the expected therapeutic benef bryotoxic effects have been seen in animal studies at doses about 10 times the maximum ommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely o served if INDERAL is administered. The added catecholamine blocking action of this dru then produce an excessive reduction of the resting sympathetic nervous activity. Occasi the pharmacologic activity of INDERAL may produce hypotension and/or marked brady resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be served at regular intervals. The drug should be used with caution in patients with impaire or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypote paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytoper purpura

Central Nervous System: lightheadedness; mental depression manifested by insomni tude, weakness, fatigue; reversible mental depression progressing to catatonia; visual d bances; hallucinations; an acute reversible syndrome characterized by disorientation for and place, short term memory loss, emotional lability, slightly clouded sensorium, and de creased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, stipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with ac and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purp

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, ous membranes and conjunctivae reported for a beta blocker (practolol) have not been c sively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe he ease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg three or f times daily, before meals and at bedtime, dosage should be gradually increased at three seven day intervals until optimum response is obtained. Although individual patients may spond at any dosage level, the average optimum dosage appears to be 160 mg per day. angina pectoris, the value and safety of dosage exceeding 320 mg per day have not bee established.

If treatment is to be discontinued, reduce dosage gradually over a period of several we (See WARNINGS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit ad quate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING SURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPO TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THER EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE)

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE

HOW SUPPLIED

INDERAL

TABLETS (propranolol hydrochloride)

No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 1(1,000. Also in unit dose package of 100.

No. 462—Each scored tablet contains 20 mg of propranolol hydrochloride, in bottles of 1(1,000. Also in unit dose package of 100.

No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 1(1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 1(1,000. Also in unit dose package of 100.

INJECTABLE

No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

References: 1. Dagenais, G.R., Pitt, B., and Ross, R.S.: Am. J. Cardiol. *28*:10 (July) 1971. 2. Ginn, W.M., and Orgain, E.S.: J.A.M.A. *198*:192 (Dec. 12) 1966. 3. Zeft, H.J., Patterson, and Orgain, E.S.: Arch. Intern. Med. *124*:578 (Nov.) 1969. 4. Dunér, H., and Pernow, B.: Ac Med. Scand. *194*:517 (Dec.) 1973. 5. Zsotér, T.T., and Beanlands, D.S.: Arch. Intern. Med. *124*:584 (Nov.) 1969. 6. Wiener, L., Dwyer, E.M., and Cox, J.W.: Circulation. *39*:623 (May) 7. Shand, D.G.: Drug Therapy *8*:53 (July) 1978. 8. Cohen, L.S., in Braunwald, E. (ed): Beta Adrenergic Blockade, A New Era in Cardiovascular Medicine: Proceedings of an Internat Symposium, New York, Excerpta Medica/Elsevier, 1978, pp. 143-151.

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WEDNESDAY, MARCH 18, 1981
PM
EXERCISE PHYSIOLOGY
4:00-5:00

EFFECTS OF BEDREST DECONDITIONING ON EXERCISE VENTRICULAR FUNCTION IN MIDDLE-AGED MEN

Joseph Hung, MD, Danielle Goldwater, MD, Victor Convertino, James McKillop, MD, Michael Goris, MD, Robert DeBusk, MD, FACC, Stanford University Medical School, Stanford, Ca.

To evaluate the effects of 10 days' bedrest (BR) on the ventricular response to exercise, 10 healthy men 50±4 years underwent equilibrium gated blood pool scanning during multistage supine and upright bicycle ergometry performed immediately pre and post BR. During all supine and upright exercise, subjects completed at least 3 minutes of a workload equivalent to 75% of their predetermined maximal workload of 1108±49 kgm/minute. RESULTS: Following bedrest, total body weight declined by 1.5 kg ($p<0.05$); resting supine left ventricular (LV) end-diastolic volume by echogram declined 17% ($p<0.05$); maximal oxygen consumption declined 6% during supine effort (NS) and by 15% during upright effort ($p<0.05$).

	SUPINE			UPRIGHT		
WORKLOAD	REST	25%MAX	75%MAX	REST	25%MAX	75%MAX
HR PreBR	71	99	143	80	108	154
PostBR	73	100	150	96†	126‡	166†
EF PreBR	60	66	72	68	74	76
PostBR	75‡	80‡	82†	75*	81*	83*

Pre vs post BR: *p< 0.05 †p< 0.01 ‡p< 0.001

CONCLUSION: In healthy middle-aged men following 10 days' bedrest: 1) the capacity for supine effort is maintained by an increase in ejection fraction which offsets a diminished left ventricular volume. 2) The capacity for upright effort declines despite an increase in ejection fraction and heart rate. 3) This indicates that orthostatic stress, not ventricular dysfunction, is the major cause of reduced exercise tolerance immediately following bedrest.

SIMILARITY OF THE HEMODYNAMIC RESPONSES TO STATIC AND DYNAMIC HANDGRIP

Steven F. Lewis, PhD; W. Fred Taylor, MS; Bruce C. Bastian, MD; C. Gunnar Blomqvist, MD, FACC, Southwestern Medical School, Dallas, Texas.

The salient hemodynamic effect of static exercise is a pressor response persisting even during combined β-adrenergic and vagal blockade. The response to dynamic exercise has been considered distinctly different with little change in mean blood pressure ($\overline{BP}$). A large increase in cardiac output (CO) is matched by a marked decrease in total peripheral resistance (TPR). However, these concepts are based on comparisons of small muscle static exercise (handgrip) vs large muscle dynamic exercise (treadmill). In the present study active muscle mass was equalized in 6 healthy men performing static handgrip and dynamic handgrip to fatigue (6 min) in the sitting position without drugs and after combined autonomic blockade (metoprolol + atropine). Mean differences Rest-exercise ± SE were:

Mode of Contraction	Condition	ΔHR (bpm)	ΔCO (l/min)	Δ$\overline{BP}$ (mmHg)	ΔTPR (units)
Static	Control	13±1	1.5±.7	28±1	1.6±1.2
	Blockade	0±1	.4±.3	21±6	2.2±1.4
Dynamic	Control	20±6	2.0±.2	34±4	.7±0.3
	Blockade	-2±1	1.4±.2	22±5	.8±1.0

The typical fall in TPR seen in treadmill exercise did not occur in dynamic handgrip. A significant ($p<0.05$) increase in $\overline{BP}$ occurred irrespective of mode of contraction and condition although autonomic blockade abolished Δheart rate (HR) and attenuated ΔCO. Conclusion: The mode of contraction is a minor determinant of the hemodynamic response during static and dynamic effort involving identical small muscle groups.

ECHOCARDIOGRAPHIC CHANGES DURING A 1 YEAR EXERCISE PROGRAM IN PREVIOUSLY SEDENTARY MIDDLE AGED MEN

Dennis M. Davidson,MD; Richard L.Popp,MD,FACC; William L. Haskell,PhD; Peter D. Wood,DSc; Steven Blair,PED; Ping Ho, MA; Elizabeth London,BA. Stanford University, Stanford,Ca.

To examine changes in cardiac dimensions and function during a 1 year exercise program, 81 sedentary men, aged 35-55, free of cardiac disease, were randomized into supervised exercise (n=48) and control (n=33) groups. M-mode echocardiograms were done at entry, 3 months, and 1 year. In 35 men (43%), all 3 echocardiograms were of sufficient quality for accurate analysis. Of the 35 men, 20 were in the exercise group, and ran 2-34 km weekly.

These variables had significant changes: LV internal dimensions at end diastole (LVd) and end systole (LVs), stroke volume(SV)(LVd^3-LVs^3), LA diameter, resting heart rate (HR) and estimated LV mass. P values were identical for absolute, percentage and (absolute ÷ BSA) changes.

	EXERCISE			CONTROL			p of Δ at	
	Entry	3mos	Year	Entry	3mos	Year	3mos	Year
LVd	5.07	5.15	5.28	5.09	5.08	4.96	>.1	.001
LVs	3.14	3.22	3.23	3.21	3.13	3.09	.08	.03
LA	3.82	3.98	4.01	3.82	3.74	3.69	.06	.01
SV	99	103	114	101	101	93	>.1	.01
HR	66.4	60.9	56.5	68.9	67.2	70.7	.01	.0001
Mass	201	206	226	205	199	197	>.1	.01

There were no significant changes in percent fractional shortening, thickness or thickening of septum and posterior LV wall, or estimated cardiac output.

Conclusions: Compared to controls, middle-aged men undergoing yearlong exercise training had progressive increases in LV and LA chamber size, LV mass and stroke volume, decreased resting heart rate, and no change in fractional shortening, septum and posterior LV wall thickness or thickening, and estimated cardiac output.

EXERCISE INDUCED ARTERIAL HYPOTENSION - A NORMAL RESPONSE TO SEVERE EXERCISE

Allen F. Bowyer, MD; Lynn H. Orr, Jr., MD; Barbara L. Gilmore, East Carolina University School of Medicine, Greenville, NC.

Exercise induced hypotension (EXH) has been reported to be a sensitive indicator of coronary stenosis. This hypothesis was tested in 58 patients with angiographically documented significant coronary disease and 168 normal volunteers (age range 15-83) undergoing progressive, symptom limited treadmill or bicycle ergometer stress test. Both exercise methods began at approximately 3 METS and progressed by steps of 1-2 METS every 3 mins. to fatigue or symptom limit. Brachial artery pressure, 3 simultaneous lead ECG, heart rate, and symptoms were continuously recorded throughout exercise and 6 min. recovery.

Although the normal group was able to exercise to higher oxygen consumption, 73% of subjects in both groups demonstrated a drop of systolic blood pressure at or near their exercise limit. During fatigue limit exercise in normal subjects, 85% (80/94) between the ages of 20 and 40 demonstrated a significant drop of systolic and mean arterial pressure. This proportion was 69% (20/29), 64% (16/23), 37% (6/16), and 25% (1/4) for normal subjects aged 50, 60, 70, and 80, respectively.

EXH was found to be neither sensitive nor specific for coronary artery disease but appeared to represent a response shown by most subjects to the severe reduction of diastolic filling period at rapid heart rate.

EDNESDAY, MARCH 18, 1981
M
YPERTENSION—RESEARCH
00-5:00

E-DEPENDENT ENHANCEMENT OF VASCULAR PHOSPHOLIPID (PL) ACYLATION-REACYLATION CYCLE IN SPONTANEOUSLY HYPER- NSIVE RATS (SHRs).
therine Limas,MD and Constantinos J.Limas,MD;Veterans ministration Medical Center and the University of nnesota, Minneapolis, Minnesota.

bstrate availability is a key step in prostaglandin (PG) nthesis regulation and depends,to a large extent,on the tivity of membrane phospholipase A_2(PLase). We have com- red PG synthesis and Plase activity in aortas of SHRs d WKYs as a function of age.At 7 weeks,there is no dif- rence in either PG or Plase between the two groups.With lvancing age,aortic PG synthesis increases in both SHRs d WKYs but is significantly higher in hypertensive rats).52±0.04 nmol PGI_2/mg/15 min in SHRs at 42 wks compared 0.29±0.04 nmol/mg/15 min in WKYs,p<0.01). Plase activ- s remains unchanged in WKYs between 7 and 42 weeks, but SHRs,increases from 29±3 pmol/mg/hr to 88±6 pmol/mg/hr ring the same timer period. Maintenance of membrane in- grity in the face of increased PLase requires efficient plenishment of fatty acids into PLs. We,therefore,com- red the incorporation of ^{14}C-arachidonate(^{14}C-ara)into scular lipids of SHRs and WKYs. ^{14}C-ara esterification to PL was higher in SHRs(0.56±0.1 nmol/mg/hr vs. 0.32± 04 in WKYs,p<0.01)while labeling of neutral lipids was milar in the two groups. The pathways for removal of solecithin generated by the enhanced PLase activity were lso investigated. Lysolecithin-lysolecithin acyl trans- rase and lysolecithin acyl-CoA transferase activities d not differ in the two groups. Lysolecithinase activity, owever,was significantly higher in SHRs(751±35 pmol/mg vs 03±22 in WKYs,p<0.01).These results indicate that vascu- r PL deacylation-reacylation cycle is enhanced in SHRs cause of increased formation and removal of lysolecithin. is enhancement parallels the increase in PG synthesis d may determine substrate delivery to the synthetase.

N EXPERIMENTAL MODEL TO DEMONSTRATE OBJECTIVELY THE AS- OCIATION OF LABILE HYPERTENSION TO VASCULAR COMPLICATION
bid A. Shah, M.D.; Robert Barndt, M.D., University of outhern California, Los Angeles, CA.

he association between labile hypertension and vascular omplications has been suspected epidemiologically. In he absence of an objective method of validation, we de- igned a prospective, randomized study to investigate his quantitatively. Twenty-four New Zealand rabbits ere randomized into three equal groups. One group of 8 abbits were used as age-matched controls. Two other roups were fed a high (2%) cholesterol (Chol.) diet for months. One group of Chol. fed rabbits was given ran- om numbers of norepinephrine (NOR) infusions (1 mg per 0 minutes) daily during the fourth month of Chol. feed- ng to induce labile hypertension. Significant elevation f blood pressure (BP) compared to baseline BP was obta- ned (mean=172, range=140-190mm Hg, P<0.001). The dura- ion of NOR effect on vascular tone was assessed by serial ngiography before and after NOR infusion. Both BP and uminal diameter changed significantly during infusion, ut both returned to normal within 30 minutes, demonstra- ing the transitory effect of NOR. Risk factor levels id not differ significantly between the high Chol. and he NOR group (mean values: Serum Chol.=1800 mg%, serum riglyceride=252mg%, and systolic BP= 110mm Hg.). At au- opsy, the extent of atherosclerosis was significantly reater (P<0.025) in the NOR group (mean=76%, range 62-94), compared to the high Chol. group (mean=53%, range 25- 0%), and was reproducible (R=0.99, SEE=3%). Linear re- ression analysis revealed a significant correlation be- ween the number of NOR infusions and the atherosclerotic rea (R=0.59, P<0.005).
n conclusion, brief periods of significant BP elevations an produce accelerated atherosclerosis compared to con- rols with identical risk factors.

EFFECT OF DIETARY SODIUM AND POTASSIUM CONTENT ON SYMPATHETIC ACTIVITY IN spSHR.
Albert Schömig, MD, Rainer Dietz, MD, Wolfgang, Rascher,MD Ruth Strasser, MD, and Wolfgang Kübler, MD, Dept. of Cardiology University of Heidelberg, Germany.

Dietary sodium loading in stroke prone spontaneously hyper tensive rats (spSHR) accelerates the rise in blood pres- sure whereas a potassium rich diet causes an attenuation of the development of hypertension. Since sympathetic ac- tivity and vascular reactivity to noradrenaline (NA) is elevated in spSHR as compared to WKR, we investigated the effects of changes in dietary sodium and potassium content on these parameters. The reactivity of vascular smooth muscle to NA was enhanced following dietary sodium loading as compared to normal fed animals and rats on a diet in which sodium was partially replaced by potassium (HSP diet : 650 mmol NaCl/kg and 200 mmol KCl/kg). A high sodium diet (HS diet: 1000 mmol NaCl/kg) for a period of 14 days resulted in a rise of plasma NA concentration after cold exposition from 368 ± 53 to 842 ± 30 ng/l and of adrenali- ne (A) from 245 ± 72 to 1168 ± 357 ng/l, being markedly less pronounced in normal fed spSHR NA from 244 ± 30 to 448 ± 51 ng/ml and A from 202 ± 56 to 374 ± 49 ng/l. In addition, a supersensitivity of vasculature to NA was ob- served (ED_{50}: 1.66 ± 0.18 vs 2.4 ± 0.26 µmol NA), which was the consequence of a reduced cocaine dependent uptake (uptake 1) of NA after a high sodium diet (70 ± 3 vs 96 ± 8 pmol/min/g tissue). Feeding with the potassium substitu- ted diet (HSP) improved the diminished uptake capacity by 50% in comparison to the high sodium group. In conclusion, a high dietary content of sodium further enhances sympa- thetic activity and vascular reactivity in spSHR. This can be ascribed, in part, to a reduction of neuronal uptake of NA, wich is restored to normal by partial replacement of sodium by potassium in the diet.

ECHOCARDIOGRAPHIC EVIDENCE FOR EARLY LEFT VENTRICULAR HYPERTROPHY IN RENAL HYPERTENSIVE DOGS
Shigefumi Morioka, MD; Geza Simon, MD, Department of Medicine, University of Minnesota and V.A. Medical Center Minneapolis, MN.

To investigate the rate of development of LV hypertrophy, LV wall thickness was measured with M-mode echocardio- graphy in 10 awake male dogs for several weeks before (control) and for 6 weeks after the induction of hyper- tension. Hypertension was produced by wrapping (Wx) one kidney in silk followed 2 weeks later by contralateral nephrectomy (Nx). Echocardiographic measurements were performed 2 to 3 times weekly and were averaged. Three dogs with sham-Wx and contralateral Nx served as con- trols. Results (mean±SE) in hypertensive dogs were:

Weeks	Control	Wx 1	Wx 2	Nx 1	Nx 2	Nx3-4	Nx5-6
MAP	125	138	141*	173***	185***	185***	184**
(mmHg)	± 3	± 7	± 4	± 5	± 9	± 13	± 15
WTd	8.0	8.2	8.8***	9.5***	9.9***	10.4***	10.8***
(mm)	±0.2	±0.2	± 0.3	± 0.3	± 0.4	± 0.3	± 0.4
Dd	44	44	44	44	44	43**	43*
(mm)	±1.4	±1.3	± 1.5	± 1.6	±1.2	±1.3	±1.6

MAP is mean arterial pressure; Dd and WTd are enddiastolic LV dimension and LV wall thickness; *p<0.05, **p<0.01, ***p<0.001 (paired t test). Heart rate did not change during the study. There were no echocardiographic changes in control dogs. The change in WTd between the control period and 2 weeks after wrapping was unrelated to the change in MAP during the same time (r=0.13, N=10). LV hypertrophy is detectable by serial echocardiograms early in hypertension with minimal increases in MAP, suggesting that humoral or neurogenic factors also may contribute to its development.

WEDNESDAY, MARCH 18, 1981
PM
PEDIATRIC ECHOCARDIOGRAPHY
4:00-5:00

TWO-DIMENSIONAL (2D) ECHOCARDIOGRAPHIC IMAGING OF ATRIO-VENTRICULAR (AV) VALVES, SEPTAL STRUCTURES, AND RUDIMENTARY OUTFLOW CHAMBERS (RC) IN PATIENTS WITH UNIVENTRICULAR HEARTS (UH)

David J. Sahn, MD, FACC; Joyce R. Harder, MD; Robert M. Feedom, MD, FACC; Walter J. Duncan, MD; Richard D. Rowe, MD, University of Arizona, Tucson and University of Toronto, Canada.

In this study we used electronically or dynamically focussed high resolution 2D echo systems to image 44 patients, angiographically, surgically or autopsy proven to have UH. Thirty-three had UH of LV type. Five patients had UH of RV type. Two of these had blind trabecular pouches and no outflow from the RC. Six patients had indeterminate UH without RC. The diagnosis of UH was correctly achieved using 2D echo in all but 2 of the earliest (1974) patients. 2D echo also correctly predicted 25 of 27 with double inlet main chamber (MC), 5 patients with absent left and 12 with absent right AV connection. AV valve overriding the RC (surgically confirmed) was also correctly identified in 2. Thirty-four of 36 RC's giving rise to a great artery were identified by echo with imaging of trabecular septum, conus or outlet septum and the outlet foramen (OF). One of 2 small blind trabecular pouches was missed on echo. The other was missed on angio but was present at autopsy. UH of LV type could be predicted by an RC not coming to the crux of the heart, coarser trabeculation in the RC than in the MC and imaging of the posterior medial muscle bundle on the posterior wall of the MC. UH of RV type could be identified by the more inferior positioning of the OF, an RC coming down to the crux of the heart near the AV groove and RC with a more posterior position. RC could be identified whether left or right sided especially when using apex 4 chamber or subcostal views. 2D echo provides detailed analysis of AV valve morphology, MC morphology and RC size and position in patients with UH.

ECHOCARDIOGRAPHIC DIAGNOSIS OF ABSENT PULMONARY VALVE SYNDROME IN THE NEONATE

John P. Cheatham, MD, Larry A. Latson, MD, Howard P. Gutgesell, MD, FACC. The Lillie Frank Abercrombie Section of Cardiology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston.

Infants with absent pulmonary valve syndrome (APVS) frequently present in the neonatal period with cyanosis, heart murmur, and respiratory distress. To determine if there were unique echocardiographic features of APVS, we performed echocardiograms on 7 infants with this condition (confirmed by cardiac catheterization). The mean age was 11.8 days. By M-mode echocardiographic measurement, the right ventricle was dilated (mean, 14.3 mm) and hypertrophied. In 6 subjects the aorta was enlarged and straddled the septum. In all 7 neonates a single semilunar valve was detected. The septal motion was abnormal in 6: paradoxical in 5, markedly reduced excursion in 1. In the subject without pulmonary insufficiency clinically, septal motion was only slightly reduced. Two-dimensional echocardiograms (2-D Echo) in 3 infants demonstrated subaortic ventricular septal defect, narrowing of pulmonary annulus, and dilatation of the main pulmonary artery.

The unique features of abnormal septal motion in combination with a single overriding great artery are highly suggestive of absent pulmonary valve syndrome, and help distinguish this condition from tetralogy of Fallot or truncus arteriosus by M-mode echocardiography. Demonstration of a narrow pulmonary annulus and dilated main pulmonary artery by 2-D Echo help confirm the diagnosis.

EVALUATION OF TRICUSPID ATRESIA BY TWO-DIMENSIONAL ECHOCARDIOGRAPHY

José Colό, MD; A. Rebecca Snider, MD, FACC; Norman H. Silverman, MD, FACC, University of California, San Francisco, Ca.

We reviewed the two-dimensional echocardiograms (2DE) of 13 patients (pts) aged 6 hrs. to 25 yrs. with tricuspid atresia (TA) to determine the anatomic type according to Edwards & Burchell and to evaluate the size of the right ventricle. From the parasternal short axis view, we measured the diameters of the Ao and main PA with a computerized light pen in order to estimate the PA size and pulmonary blood flow. The 2DE findings were compared to the findings at cardiac catheterization and cinéangiography. From the 2DE, the anatomic type of TA was predicted correctly in 10 pts and incorrectly in 2 pts. In one pt, the echocardiogram was technically inadequate for anatomic classification. In 11 of the 13 pts, the right ventricular size estimated from the 2DE was identical to the right ventricular size estimated from angiography. The ratio of the diameters of the Ao and PA (Ao/PA) measured from the 2DE (Ao/PA 2DE) was comparable to the ratio of the diameters of the Ao and PA measured from the angiogram (Ao/PA angio)($r = 0.91$, SEE $= \pm 0.21$). The PA diameter measured from the 2DE and corrected for body surface area (PA/BSA 2D) correlated well with the ratio of the pulmonary and systemic blood flows (Qp/Qs) determined at catheterization ($r=0.80$, SEE $= \pm 0.56$). The 2DE was an accurate indicator of the anatomic type of TA as well as the size of the right ventricle, pulmonary artery, and pulmonary blood flow. 2DE provides a safe, non-invasive technique for the serial evaluation of patients with TA both before and after surgical intervention.

TWO DIMENSIONAL ECHOCARDIOGRAPHIC ESTIMATION OF LEFT VENTRICULAR VOLUME IN SMALL NEWBORN LAMB HEARTS.

Barry Baylen, MD, FACC; Yoshiro Yoshida, MD; Ismael Mena, MD; George Emmanouilides, MD, FACC, Harbor-UCLA Medical Center, Torrance, CA

Two dimensional echocardiographic (2DE) estimations of left ventricular volume (LVvol) correlate well with angiographic volumes in older infants and children. However, such correlative studies are obviously difficult to obtain in newborn and preterm infants.

Hence, we evaluated 2DE for LVvol estimation in preterm and term postmortem lamb hearts (130 day gest-term-3wk). The volume of 22 fixed LVs were measured directly (range 0.8-9.9cc). The LVs were imaged in short and "long" axis views (rt. ant. oblique equivalent) in a saline filled chamber using a Toshiba phased-array ultrasonoscope. Forty-four 2DE images were digitized using an Informatek Simis 3 computer and LVvols were calculated using the following standard methods: (1)single plane area-length (A-L), and (2)Simpson's reconstruction. Directly measured LVvols(Y) were compared with 2DE calculated LV vol(X) using linear regression analyses.

		*r=	p=
A-L	$Y(Vol) = 0.79X_{echo}+.52$	0.96	<0.001
Simpson	$Y(Vol) = 0.85X_{echo}+.50$	0.95	<0.001

Excellent correlations* were obtained between measured and 2DE calculated left ventricular volumes.

The data suggest that (1)accepted geometric methods predict left ventricular volumes for even small preterm hearts, and (2)two dimensional echocardiography should ultimately provide good estimates of left ventricular volumes in the human newborn infant.

WEDNESDAY, MARCH 18, 1981
PM
MONITORING IN NON-ATHEROMATOUS DISEASES
4:00-5:00

CARDIAC RHYTHM, ARTERIAL PRESSURE, AND URINARY CATECHOLAMINES IN HYPERTENSION WITH AND WITHOUT LEFT VENTRICULAR HYPERTROPHY.

Franz H. Messerli, MD, FACC; Louis B. Glade, MD; David G. Elizardi, MD; Gerald R. Dreslinski, MD; Francis G. Dunn, MD; Edward D. Frohlich, MD, FACC. Ochsner Medical Institutions, New Orleans.

Continuous ambulatory EKG and arterial pressure (Delmar Avionics) were recorded for 24 hr in 20 normotensive subjects (NTS), 11 patients with borderline hypertension (BHT), 15 with uncomplicated (normal EKG) essential hypertension (EHT), and 6 with left ventricular hypertrophy (LVH) on EKG, all untreated. Urinary concentrations of epinephrine, norepinephrine, and dopamine were simultaneously measured over 4 successive 4-hr periods and one 8-hr period. Results were as follows (mean ±1SEM).

	Arterial pressure	APC's	VPC's	Heart Rate
NTS	110±2.5/79±1.4	7.4±4.8	5.0±2.9	77±3
BHT	127±2.3/90±2.2	4.2±4.0	6.4±4.1	78±2
EHT	145±4.4/102±2.8	5.7±4.4	8.6±5.8	75±4
LVH	155±6.8/104±3.5	4.8±4.0	517±290*	80±5

*p<0.01 vs ETH

Epinephrine, norepinephrine, and dopamine excretion were comparable between the four groups and showed a significant (p<0.02) nocturnal fall. However, urinary catecholamines did not correlate with prevalence of APC's or VPC's, absolute values or variability of heart rate and arterial pressure. It is concluded that hypertensive patients with EKG evidence of LVH have a higher prevalence of VPC's (but not APC's) and thus are at a higher risk of ventricular arrhythmias and sudden death than patients with a similar arterial pressure without LVH. Urinary catecholamines are not causally related to prevalence of ectopic beats, diurnal fluctuation or variability in heart rate or arterial pressure.

EFFICACY OF 24 HOUR AMBULATORY ECG MONITORING AS A PREDICTOR OF SUDDEN DEATH IN HYPERTROPHIC CARDIOMYOPATHY

Barry J. Maron, MD, FACC, Daniel D. Savage, MD, Stephen E. Epstein, MD, FACC, NHLBI, Bethesda, Md.

Sudden death is a not rare sequelle of the natural history of pts with hypertrophic cardiomyopathy. However, the mechanism of these catastrophic occurrences is unknown. Our previous 24 hr ambulatory ECG monitoring studies showed in 99 pts with hypertrophic cardiomyopathy (who were not taking cardioactive medications), a particularly high prevalence (i.e., 66%) of high-grade (Lown, grade 3 or higher) ventricular arrhythmias, and specifically ventricular tachycardia (VT) (i.e.19%). Since the significance of these arrhythmias in identifying pts at high- risk for sudden death is not known, clinical outcome was followed prospectively for 3 yrs in these pts. Of the 84 pts who did not undergo ventricular septal myotomy-myectomy, 6 died suddenly, 1 died of chronic heart failure and 77 survived. Prevalence of sudden death during the follow-up period was the same in pts with high-grade arrhythmias other than VT (1 of 37 or 3%) and in pts with no or low-grade arrhythmias (1 of 29, or 3%). However, occurrence of sudden death was significantly more common in pts with VT on their 24-hr ECG (4 of 17 or 24%) than in pts without VT (2 of 66 or 3%; p< 0.02). We conclude: 1) high-grade ventricular arrhythmias are common on continuous 24-hr ECG in pts with hypertrophic cardiomyopathy and 2) while sudden death is relatively uncommon in patients with high-grade ventricular arrhythmias other than VT, the finding of VT on 24-hr ECG identifies a subgroup of patients at high-risk for sudden death; 3) 24 hr ECG monitoring should be performed in pts with hypertrophic cardiomyopathy and antiarrhythmic therapy begun if VT is identified.

PROLONGED QT INTERVAL AND AUTONOMIC IMBALANCE: A CLUE FOR THE PREVENTION OF SUDDEN DEATH IN MITRAL VALVE PROLAPSE

Paolo E. Puddu, MD; Julio F. Tubau, MD; Ryszard Król, MD; Jacques de Champlain, MD, PhD; André Pasternac, MD, FACC, Montreal Heart Institute and University of Montreal, Montreal, Quebec

Sudden death (SD) has been reported in pts with mitral valve prolapse (MVP) but the underlying mechanism remains unclear so that prevention cannot be easily achieved. Since an autonomic imbalance may lead to a prolonged QT interval and thus increase the risk for SD, we compared the heart rate corrected QT (QTc) and the levels of total plasma catecholamines (TPC) and norepinephrine (NE) in 15 symptomatic pts with documented MVP (mean age 48±3 years) and in 19 normal subjects (mean age 41±2 years). QT interval was calculated in lead II; TPC and NE were measured in the resting state, after an 8 hour fast, all medications being discontinued for at least four days. MVP pts were divided into 2 groups: A) QTc <440 ms; B) QTc ≥440 ms.

	NORMALS (N19)		A (N10)		B (N5)
QTc (ms)	398±4	* *	423±5	* *	453±5
TPC (pg/ml)	348±17	*	420±35	*	619±104
NE (pg/ml)	242±25	*	350±31	N S	376±52

$\bar{x}$ ± SEM; * p<0.05; ** p<0.005 (variance analysis)

Thus, MVP pts with prolonged QTc (≥440 ms) have the highest TPC and NE levels. This provides a rationale for adrenergic blockade in that subset of pts with prolonged QTc who may be at greater risk of sudden death.

DISTRIBUTION OF BODY SURFACE ECG POTENTIALS IN FAMILIAL QT INTERVAL PROLONGATION

J.A. Abildskov, M.D., F.A.C.C.; G. Michael Vincent, M.D., F.A.C.C.; A. Kerry Evans, Ph.D., Mary Jo Burgess, M.D., University of Utah, Salt Lake City, Utah

Body surface distributions of ECG potentials were determinded for 11 patients (age 5-37 years) with familial QT interval prolongation. Data were obtained with a 32 lead system that permits accurate prediction of total thoracic potentials (avg rms voltage error 35 μV). Leads were sampled simultaneously at 1 msec intervals and computer processed to yield serial isopotential maps and maps of ST-T and QRST deflection areas on a 12 x 16 matrix. Serial isopotential maps had more negative than normal anterior poles and vertical null lines. Quantitative analysis of ST-T and QRST area distributions showed characteristic features that help define pathophysiology of familial QT interval prolongation. Average ST-T and QRST area distributions were determined from 200 normal adult subjects and subtracted from those of prolonged QT interval patients. Resulting difference maps had prominent negative poles on the anterior or anterolateral thorax in 9 of the 11 cases. Peaks differed from the average normal by 1 to 4 standard deviations (SD) for the ST-T (avg 2.5) and 1 to 3 SD for the QRST (avg 2.1). It is unlikely findings were due to age differences of normal and test groups since 6 patients were above 25 years and none of the younger patients showed the juvenile pattern of inverted T waves in mid-precordial leads. Findings suggest prolonged repolarization in anterior and lateral ventricular walls which are normally innervated by right sided sympathetic fibers. Since denervation prolongs repolarization, findings are compatible with deficient right sympathetic effects which is one of the possible mechanisms of familial QT prolongation.

WEDNESDAY, MARCH 18, 1981
PM
NUCLEAR CARDIOLOGY—DETECTION AND QUANTITATION OF MYOCARDIAL ISCHEMIA
4:00-5:00

β^+-PROBE DOCUMENTATION OF A DIRECT RELATION BETWEEN CLEARANCE OF ^{11}C-PALMITATE AND MYOCARDIAL METABOLISM
Rene A. Lerch, MD; H. Dieter Ambos; Steven R. Bergmann, PhD; Michel M. Ter-Pogossian, PhD; Burton E. Sobel, MD, FACC, Washington University, St. Louis, Missouri

To delineate the extent to which myocardial clearance of the positron emitter, ^{11}C-palmitate, depends on metabolism per se in open chest dogs, we developed a β^+ probe (10 mm diameter, 3.0 mm thick plastic scintillation crystal) to monitor β^+-radiation time-activity curves in selected subepicardial regions defined by the probe's dimensions and the short range of β^+ particles in tissue (4.0 mm for ^{11}C, 6.2 mm for ^{15}O). Annihilation gamma radiation contributed < 6% to observed count-rates, precluding contamination of results by tracer in the ventricular cavity or outlying myocardial regions. Nine dogs were subjected to intracoronary injection of 4 to 6 mCi of ^{11}C-palmitate and 1 mCi of $H_2{}^{15}O$ under conditions of controlled perfusion of the left anterior descending coronary artery via a femoral artery shunt. ^{11}C-palmitate clearance was monoexponential from 5 to 12 minutes after injection ($r = .99 \pm .003$ (SE)) with an average rate constant of $.076 \pm .012$ min^{-1} and with duplicate determinations agreeing within $6.3 \pm 2.0\%$. Duplicate myocardial blood flow determinations calculated from monoexponential clearance of $H_2{}^{15}O$ agreed within $3.6 \pm 0.7\%$. Perfusion with hypoxic blood at the same flow decreased clearance of ^{11}C-palmitate by > 70%. These results, based on detection of β^+ radiation in vivo rather than simply gamma radiation in isolated hearts demonstrate that externally detectable, decreased clearance of ^{11}C-palmitate is a direct consequence of impaired aerobic metabolism secondary to anoxia.

QUANTITATION OF MYOCARDIAL PERFUSION IN MAN USING OXYGEN-15 AND POSITRON TOMOGRAPHY.
Roger M.Allan, FRACP, Terry Jones, MSc, Christopher C.G. Rhodes, MSc, Jon D. Heather, Attilio Maseri, M.D. FACC and Andrew P.Selwyn, MRCP. MRC Cyclotron Unit and Royal Postgraduate Medical School, Hammersmith Hospital, London.

The non-invasive quantitation of regional myocardial perfusion (RMP) is an important goal in clinical cardiology. Steady state theory and inhalation techniques using $C^{15}O_2$ ($t_{½}$=123 sec) to label circulating H_2O have been used with positron tomography to measure cerebral blood flow. The difficulty in applying this methodology to the myocardium is the interference from radioactivity within the vascular compartment. To overcome this the vascular space was defined during the inhalation of $C^{15}O$. Using these principles, serial emission tomograms of the myocardium were performed in 8 anaesthetised dogs during continuous inhalation of $C^{15}O_2$. The vascular component of this signal was identified by tomography during inhalation of $C^{15}O$ and this data subtracted from the $H_2{}^{15}O$ data. The arterial blood concentrations of $H_2{}^{15}O$, required for calculations, were measured in a well-counter. A range of blood flows was studied using pharmacological interventions. Partial volume correction made using measurements from anatomical dissection correlated well with a new in-vivo approach using transmission scan data ($P<0.01$).

The results show images that clearly delineate the regional myocardial distribution of $H_2{}^{15}O$ with myocardial: lung ratio = 8.2 ± 0.9(SD). Calculated perfusion values ranged from 0.51 to 3.70 mls/gm/min. In similar studies in 5 patients resting values for RMP were calculated and ranged from 0.42 to 0.65 mls/gm/min. Myocardial oxygen consumption using $^{15}O_2$ was also studied.

These results suggest that RMP (ml/gm/min) may be measured non-invasively in man using positron tomography and inhalation of short-lived radioactive gases.

EVALUATION OF INFARCTED AND ISCHEMIC MYOCARDIUM WITH 18-FLUORODEOXYGLUCOSE, $^{13}NH_3$, AND POSITRON COMPUTED TOMOGRAPHY.
Robert C. Marshall, MD, Henrich R. Schelbert, MD, Michael E. Phelps, MD, Jan H. Tillisch, MD, Eberhard Henze, MD, Sung C. Huang, MD, UCLA School of Medicine, Los Angeles, CA.

To evaluate the possibility of non-invasively identifying both ischemic (Is) and infarcted myocardium, indices of basal myocardial perfusion (MP) and metabolic rate for glucose (MMRGlc) were analyzed in 7 patients (pts) 3-9 days post infarction and in 2 pts with angina decubitus using 18-fluorodexoyglucose (FDG), $^{13}NH_3$ (NH), and positron computed tomography (PCT). Experimental evidence suggests that Is MMRGlc does not decline linearly with blood flow and that an absolute increase in MMRGlc is observed in supply-demand imbalance if flow is maintained. Since the ratio of MMRGLC to MP should be greater in Is than nonIs and dead tissue, the degree of dispersion of the FDG/NH ratio, expressed as % variation about a medium value, was used to identify Is myocardium. Of 12 remote and acute infarcts, qualitative analysis of both FDG and NH images correctly localize 10. In 6 pts, 5 of whom had no clinical evidence of continued Is, the mean and maximal variability of FDG/NH were 12.5±3.8% and 29.7±8.5%, respectively. In 3 pts, all with additional clinical evidence of Is, the mean and maximal variability were 33.7± 17% and 116±52%. We conclude that these results encourage further investigation into the use of FDG, NH and PCT to identify both ischemic and infarcted myocardium.

POSITIVE LABELING OF ISCHEMIC MYOCARDIUM: A NEW APPROACH IN PATIENTS WITH CORONARY DISEASE.
Andrew P.Selwyn, MRCP, Roger M.Allan, FRACP, Victor Pike, PhD., Kim Fox, MRCP, Attilio Maseri, FACC. Hammersmith Hospital and MRC Cyclotron Unit, London, UK.

Positron labeling of natural substrates with quantitative tomography in-vivo provides a unique opportunity to label and study the anaerobic processes jeopardising ischemic myocardium. Carbon-11-acetate (^{11}C-Ac) has been produced for peripheral intravenous injection and 0.125 - 0.2 mCi/kg body weight was given to 8 healthy subjects (4 at rest and 4 during exercise). Serial emission tomograms showed a monoexponential decrease in the regional myocardial (RM) activity between 3 and 12 min. Washout in the 4 subjects at rest showed a $t_{½}=8.3 \pm 0.74$ min(SD), a rate constant = 0.084 ± 0.007 and a regional myocardial coefficient of variance (CV) of 8.7% (mean). The 4 subjects during exercise showed a $t_{½}=7.9 \pm 0.47$ min, a rate constant = 0.087 and a CV = 2.8%. 5 patients with angina and coronary disease were given 0.2 mCi/kg of ^{11}C-Ac 1 to 2 min before ischemic changes in the ECG during a standardised exercise test. Serial emission tomograms showed a homogeneous initial RM distribution of activity at 3 min. Thereafter the RM washout from the affected myocardium ($t_{½}$=10.1 min,(mean), rate constant, 0.069) was significantly different ($P=<0.01$) from the remote myocardium ($t_{½}$= 7.7 min,(mean), rate constant = 0.09). RM washout of activity was thus heterogeneous (CV=16%). The acutely ischemic myocardium was easily identified being positively labeled for up to 12 min after the normalisation of the ECG. The ratio of ischemic to remote myocardium at 12 min was 1.8:1. The data suggests that there are prolonged disturbances of ischemic myocardium beyond the ECG and symptomatic evidence. Natural substrates labeled with positron nuclides provide a new approach for the positive identification and investigation of acutely ischemic myocardium in patients.

THURSDAY, MARCH 19, 1981
AM
PHARMACOLOGY: NEW ANTIARRHYTHMIC DRUGS AND CONCEPTS
8:30-10:00

SUCCESSFUL CONTROL OF THE CHRONIC FORM OF SUPRAVENTRICULAR TACHYCARDIA WITH ORAL VERAPAMIL HYDROCHLORIDE

Ruey J. Sung, MD, FACC; Candy Raphan, RN; Zulfikar Juma, MD, Arrhythmia Control Clinic, Department of Medicine, University of Miami, Miami, Florida.

Chronic supraventricular tachycardia (SVT), in contrast to the paroxysmal form of SVT, is characterized by its almost incessancy interposed by short periods of sinus rhythm. Verapamil hydrochloride (V) was used to treat 12 patients(pts) with the chronic form of SVT at rates ranging from 140 to 180 beats per minute. Three pts had sinus nodal reentrant tachycardia, 4 pts atrioventricular (A-V) nodal reentrant tachycardia and 5 pts A-V reciprocating tachycardia involving concealed retrograde conducting bypass tracts. All 12 pts were symptomatic and were resistant or intolerant to digitalis, propranolol, quinidine, procainamide and disopyramide used alone or in various combinations. V was given orally at dosages ranging from 320 to 800 mg per day and all pts were followed at bimonthly intervals at our arrhythmia control clinic. With a follow-up period of 5-23 (mean 14.6) months, all 12 pts had symptomatic improvement. Repeated holter monitoring during V therapy demonstrated that 8/12 pts manifested only atrial echo phenomenon and 4/12 pts slow, short-lived SVT at rates of less than 100 beats per minute. The therapeutic plasma V concentrations measured 112 to 572.6 (mean 232 ± 127) ng/ml. One pt developed headache, 1 pt constipation and 2 pts peripheral edema presumably due to venous relaxation effect of V. Each of these side effects was mild and clinically manageable. We conclude that oral V therapy is safe and effective for pts with the chronic form of SVT. In addition, this study suggests that V therapy may be tried before contemplating pacemaker therapy or surgical intervention in these pts.

ROLE OF SERUM T4 AND REVERSED T3 IN MONITORING ANTIARRHYTHMIC EFFICACY AND TOXICITY OF AMIODARONE IN RESISTANT ARRHYTHMIAS

Koonlawee Nademanee, MD; S. Melmed, MD; JoAnn Hendrickson, BS; A.W. Reed, MS; Jerome M. Hershman, MD; Bramah N. Singh MD, FACC, Wadsworth VA Hospital, Los Angeles, California

Amiodarone (Am), a potent iodinated antiarrhythmic drug, increases serum T4 and reversed T3 (rT3) without producing clinical hyper or hypo-thyroidism. Thus, T4 and rT3 and QTc were measured serially in 15 euthyroid pts with resistant (to other agents) cardiac arrhythmias (7 ventricular, 8 atrial) before, during and after withdrawal of Am (600-1000 mg/day) therapy and correlated with drug toxicity and antiarrhythmic efficacy (AE), documented by serial 24 hr Holter analysis. Results (mean±S.D.; *p<0.001):

	T4 µg/dl	rT3 ng/dl	Q-Tc
Predrug	7.8±2.2	37±7	0.44±0.03
3 week	12.1±2.8	67±22	0.48±0.02
Peak (2-5 wk)	15.9±3.2*	84±21*	0.49±0.04*
6 wk after drug stopped	9.5±1.9	55±5.5	0.46±0.04

Amiodarone increased T4 and rT3 in all patients; a linear correlation was found between an increase in rT3, AE and Q-Tc. AE was invariably associated with rT3 level >55 ng/dl and drug side effects with >100 ng/dl. The correlation with T4 was less striking. On drug withdrawal, side effects disappeared when rT3 fell <100 ng/dl and arrhythmias returned at levels <55 ng/dl.
Conclusions: 1) Serum rT3 provides a sensitive index to monitor efficacy (55-100 ng/dl) and toxicity (>100 ng/dl) of Amiodarone and 2) the data provides evidence for the drug producing a selective inhibition of T3 action on the heart as a potential basis for its antiarrhythmic effect.

ORAL FLECAINIDE ACETATE FOR ELIMINATION OF VENTRICULAR ARRHYTHMIAS IN MAN

Jeffrey L. Anderson, MD, FACC; James R. Stewart, MD; Benjamin A. Perry, MD; Daniel D. Van Hamersveld, MD; Theresa A. Johnson, RN; Bertram Pitt, MD, FACC, University of Michigan, Ann Arbor, Michigan

In order to determine the antiarrhythmic efficacy and safety of oral flecainide acetate (FA) in man, a placebo controlled dose-ranging and short-term oral maintenance study was undertaken in 13 patients (pts) with chronic, ventricular ectopy (VE) of frequency >600 VE/12 hrs. During a 2 day placebo control period, 11/13 maintained stable VE frequency (mean 11,254/12 hr,range 653-35,551) and entered dose-ranging. Dosage was increased in increments at 3 day intervals from 100-300 mg/12 hr until 95% VE suppression, limiting side effects, or dosage maximum was attained. Ten pts completed dose-ranging, and pt 11 experienced a transient ischemic attack and was excluded. Of the 10 pts, 9(90%) were complete responders (CR)(mean suppression 98.7%, range 96.1-100%), and one responded partially (68% suppression). Repetitive VE was totally eliminated in all 10 pts. Pt 11 showed 77% VE suppression on 100 mg/12 hr before exclusion. Of CR, 2 pts ended dose-ranging successfully at 100 mg, 5 at 200 mg, and 2 at 250mg/12 hr. Average dose calculated to achieve 95% suppression was 169 mg/12 hrs. A 3 day placebo-controlled drug washout period was accompanied by a significant return in VE in each of the 9 CR. VE first recurred at 21.9 hrs (range 7-40), and by 3 days VE averaged149.6% of control frequency. During the subsequent outpt trial, FA remained highly effective with total and average VE suppression of 98.0% and 94.6%, respectively. ECG response included prolongation ($p<0.01$) of PR(16.5%) and QRS (10.6%). Echocardiographic CI was unchanged. FA was well tolerated except for headache in 2 pts. Thus FA appears to be a highly effective antiarrhythmic in man.

FLECAINIDE ACETATE, A NEW ANTIARRHYTHMIC AGENT: DOSE-RANGING AND EFFICACY STUDY

Morrison Hodges, MD, FACC; J. Mark Haugland, MD; Gregory Granrud, MD; Richard W. Asinger, MD; Frank L. Mikell, MD; Jeananne Krejci, RN. Hennepin County Medical Center and the University of Minnesota, Minneapolis, MN.

Flecainide acetate (R-818) is a new antiarrhythmic agent with Class I properties. Potential advantages include a long plasma half-life (ave: 14 hr); effectiveness by both oral and IV routes; efficacy at relatively small doses; and few serious side effects noted to date. We evaluated flecainide with a single-blind dose-ranging and efficacy study in 9 patients with frequent ventricular ectopic depolarizations (VEDs). Patients were hospitalized and the ECG was monitored continuously by tape recordings which were analyzed quantitatively in a blinded fashion. Two days of placebo BID were followed by three increasing oral doses of flecainide (100, 200 and 300 mgm BID for 3 days each) until complete suppression or the 300 mgm BID dose was reached; 3 days of placebo BID were then observed to assure return of baseline rhythm and to evaluate plasma pharmacokinetics. During the 2-day control period, the patients averaged 15.2 VEDs/min (range 1.3-50.0), and all patients were observed to have complex ventricular arrhythmias (> Lown Class II). At the most effective dose (200 mgm BID in 6 pts, 300 mgm BID in 3 pts), average VED suppression was 96.0% (range 77.9%-100%), with 6 of the 9 achieving 100% suppression. During placebo washout, VED return averaged 146% of control. Outpatient treatment resulted in average suppressions of 99.6% and 99.5% at 1 and 2 wks, respectively. There were no significant changes in blood pressure or heart rate, but the PR, QRS and QTc intervals increased by 29%, 24% and 7% respectively ($p < .05$ for all). Observed side effects were an occasional sense of unsteadiness (4 pts), transient blurring of vision (1 pt), and a sense of warmth (1 pt). No side effect was serious enough to require discontinuation of drug. We conclude that oral flecainide, 200 or 300 mgm BID, is highly effective at suppressing VEDs and complex ventricular arrhythmias. Side effects in these 9 pts were minimal.

DOSE RELATED HAEMODYNAMIC EFFECTS OF INTRAVENOUS ENCAINIDE.

Jennie M.Metcalfe M.R.C.P.,Kieran M. Daly, M.R.C.P.I., Lynne Atkinson BSc,Mark Monaghan, David E.Jewitt F.R.C.P.
Department of Cardiology, King's College Hospital, London, U.K.

The acute haemodynamic and metabolic effects of intravenous Encainide (E) in cumulative doses of 1.0 and 2.0 mg/Kg infused over 15 minute periods were measured in 14 patients with obstructive coronary artery disease. Baseline right and left heart pressures, left ventricular (LV) dp/dt and thermodilution cardiac output and coronary sinus blood flow, myocardial lactate and oxygen extraction were recorded. Measurements were repeated after completion of the 1.0 and 2.0 mg/Kg infusions of E and 30 minutes later.
On completion of the 1.0 and 2.0 mg/Kg cumulative infusions of E significant dose related falls occurred in cardiac index (2.7 to 2.3 to 2.2 L/min/m^2 $p< 0.02$), LVdp/dt max. (1595 to 1405 to 1276 mmHg/sec. $p< 0.01$) with a rise in peripheral resistance (21 to 25 to 26.5 Wood units $p< 0.02$) and coronary sinus blood flow (113 to 126 to 133 mls/min. $p< 0.005$). Coronary vascular resistance fell (0.90 to 0.79 to 0.76 units $p< 0.05$). The fall in LVdp/dt max. persisted for 30 minutes after E 2.0 mg/Kg (1595 to 1381 mmHg/sec. $p< 0.05$).
Minor and insignificant changes only occurred in heart rate, left ventricular end-diastolic pressure and myocardial lactate and oxygen extraction. Plasma E levels were in the therapeutic anti-arrhythmic range.
The dose related cardiac depressant effects observed with intravenous E indicate the need for caution when doses above 1.0 mg/Kg are used particularly in the presence of LV dysfunction.

ELECTROPHYSIOLOGIC EFFECTS OF PROPAFENONE ON CANINE ISCHEMIC CARDIAC CELLS

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Electrophysiologic effects of the new antiarrhythmic drug propafenone (P), (2-(3-propylamino)-2-(hydroxy)-propoxy-3-phyenylpropiophenone HCl) were studied by conventional microelectrode technique in two types of preparations from 24-hour-old myocardial infarction in dog: 1)epicardial strips containing myocardial cells (M) from ischemic and normal zones, 2) endocardial strips containing ischemic Purkinje fibers (PF). Of the concentrations tested, (0.1 mg/L - 25mg/L), the most effective dose range was 2-4mg/L. P resulted in a concentration-dependant increase in threshold of stimulation, slowing of conduction and reduction of amplitude, overshoot and V max of action potentials of M and PF but had no effect on resting membrane potential. These effects were more marked on depressed ischemic M and PF. We have recently shown that abnormal automaticity seen 24 hours following MI in dogs is due to triggered automaticity (TA), (Circulation, In press). In endocardial preparations from 24-hours-old MI, TA (rate 60-120/min) arising from delayed after depolarization (DAD) was consistently induced in depolarized ischemic PF by a critical cycle length during regular pacing or premature stimulation and only when DAD attained threshold. P depressed the amplitude of DAD, slowed and inhibited TA. We conclude: 1) P has a membrane anesthetic effect with depressed ischemic cells being more sensitive, 2) P also depresses ionic currents responsible for TA in depolarized PF. 3) Actions of P could result in an antiarrhythmic effect in vivo on both reentrant activation and abnormal automaticity.

THURSDAY, MARCH 19, 1981
AM
NUCLEAR CARDIOLOGY—CLINICAL APPLICATION OF THALLIUM 201 MYOCARDIAL IMAGING
8:30-10:00

THE ADVERSE PROGNOSTIC SIGNIFICANCE OF AN ABNORMAL THALLIUM MYOCARDIAL PERFUSION SCINTIGRAM.

James Joye, MD, FACC; Joan Bogre; Kirk Huang, MD; Garrett Lee, MD; Reginald Low, MD; Patricia Takeda, MD; Lawrence Laslett, MD; Ezra Amsterdam, MD, FACC; Dean Mason, MD, FACC; Anthony DeMaria, MD, FACC, University of California, Davis, California.

No data are available which describe the prognostic significance of abnormal exercise thallium myocardial scintigrams (Tl scans). We therefore analyzed the natural history of 192 patients (pts) (mean age 55.9 yrs) followed over a mean interval of 35.5 months in whom Tl scans were performed. Of the 192 pts, 12 suffered cardiac deaths and two had noncardiac deaths. All scans were interpreted with attention to the location, size and severity of any defect and the number of standard views in which it was seen. Left ventricular dilation (LV dil) was also noted if the chamber appeared larger than 1.5 x the thickness of the posterolateral wall. Scan abnormalities were scored as a product of the percent circumference and percent loss of activity involved in the defect and expressed as the sum of defects in all three standard views. Among 31 pts with LV dil there were eight deaths compared with four of 159 pts without LV dil ($p<0.001$). Death occurred an average of 20.7 months following scanning. Of the 88 pts with exercise scans having defect scores of 30 or more eight died while none of the 84 with scores less than 30 died ($p<0.01$). While only four pts had myocardial infarction (MI) following scanning, none of 55 pts with an exercise defect score of <10 died or had a MI compared to 12 such events among 116 who had scores >10 ($p<0.025$). This study demonstrates a significantly higher mortality among pts found to have LV dil or large perfusion defects as scored by exercise Tl scan while showing no serious cardiac events following exercise scans with no or small defects.

UTILITY OF SERIAL THALLIUM IMAGING FOLLOWING DIPYRIDAMOLE

Jeffrey Leppo, M.D., Charles A. Boucher, M.D., FACC, Robert D. Okada, M.D., FACC, H. William Strauss, M.D., FACC, Gerald M. Pohost, M.D., FACC.
Massachusetts General Hospital, Boston, MA

Dipyridamole provides an alternative approach to exercise for detection of coronary artery disease (CAD) using Thallium-201 (Tl). Therefore, the presence and significance of Tl redistribution after dipyridamole was studied in 50 patients having coronary angiography, 30 with CAD and 20 normals. After 0.56 ml/kg/4 min intravenous infusion of dipyridamole, Tl was given and images in 3 views were obtained initially and after 2-3 hrs. Segmental Tl activity (3/view) was scored by 3 independent observers from 0 (no activity) to 2 (normal) using 0.5 grade steps. Using previously defined criteria for initially abnormal segments, the sensitivity was 93% (28/30) and specificity was 85% (17/20). There were 117 (43%) abnormal segments in the 30 CAD patients and 4 (2%) in the 20 normals. These 121 abnormal segments were then divided into 3 groups based on the completeness of Tl redistribution and compared to segmental wall motion as assessed by contrast ventriculography. In 34 segments with a persistent defect (no redistribution), 79% were akinetic and 97% showed either akinesis or hypokinesis; while in 58 segments with complete redistribution, only 9% demonstrated akinesis ($p<.01$).

These data suggest that serial Tl imaging after dipyridamole can detect CAD and assess myocardial viability in a manner similar to exercise Tl imaging.

THALLIUM-201 REDISTRIBUTION SCINTIGRAPHY PREDICTS THE RESPONSE TO LEFT VENTRICULAR ASYNERGIC SEGMENTS TO NITROGLYCERIN ADMINISTRATION

Alan Rozanski, MD; Daniel Berman, MD, FACC; Ronald Levy, MD; Nancy Pantaleo, RN; Jamshid Maddahi, MD; James S. Forrester, MD, FACC; Alan Waxman, MD; and H.J.C. Swan, MD, FACC. Cedars-Sinai Medical Center, Los Angeles, Ca.

Since redistribution (RDST) Tl-201 scintigraphy may reflect the extent of viable myocardium, the pattern of Tl-RDST may provide a useful noninvasive means of identifying asynergic (asyn) LV segments (segs) with latent reversibility. To test this hypothesis, 17 consecutive pts with resting wall motion (WM) abnormalities undergoing stress-RDST Tl scintigraphy and resting multiple gated equilibrium scintigraphy (MGES) with Tc-99m RBC's also underwent MGES with nitroglycerin (NTG). MGES after NTG was begun following a sustained blood pressure fall of 10mm Hg or heart rate increase of 10 beats/minute. For both Tl and MGES, anterior and 45° left anterior oblique images were divided into 5 segs. WM was assessed by a 5 point system (3=normal (nl), -1=dyskinesis). Asynergic segs with post-NTG WM=3 or by $\geq$2 from control were considered improved. Tl-RDST images, obtained 4 hours post-stress, were consensually read by 3 observers unaware of the WM results.

Of 49 asyn segs, 22 improved after NTG and 27 did not. Tl-RDST correctly predicted the WM response in 39 of the 49 segs. Tl-RDST was nl in 21 of 22 segs improving with NTG and was abnormal in 18 of 27 segs which did not improve ($p<.001$). Of note, only 1 of 19 asyn segs with nl Tl-RDST improved with NTG.

Therefore, the segmental pattern of Tl-201 redistribution scintigraphy predicts the response of asynergic myocardial segments to nitroglycerin and may thus be useful in assessing the potential reversibility of resting left ventricular wall motion abnormalities.

RELATIONSHIP OF THALLIUM-201 PERFUSION IMAGES TO REGIONAL MYOCARDIAL BLOOD FLOW IN MAN

Allen B. Nichols, MD, FACC; David K. Blood, MD, FACC; Melvin B. Weiss, MD, FACC; Paul H. Chen, MD; Paul J. Cannon, MD, FACC. College of Physicians and Surgeons, Columbia University, New York, N.Y.

Regional myocardial blood flow (RMBF) was measured at coronary arteriography in 28 patients (pts) also undergoing Tl-201 exercise and redistribution scintigraphy. Identical multicrystal scintillation cameras were used for Tl-201 scintigraphy and for measuring RMBF by the Xenon-133 clearance method. Appropriately magnified Tl-201 images (LAO projection) were superimposed on RMBF patterns. In 10 pts with normal exercise and redistribution Tl-201 images, RMBF was homogeneous at rest and during rapid atrial pacing. RMBF in the left anterior descending region did not differ significantly from RMBF in the circumflex region, either at rest (60.2±12 vrs 59.7±12 ml/100 gm·min) or during rapid pacing (82.4±22 vrs 86.2±22). Global left ventricular (LV) flow, however, ranged widely from 35 to 77 ml/100 gm·min at rest and from 45 to 114 during pacing. In 5 pts with persistent defects on Tl-201 redistribution images, resting RMBF was reduced by 19% in the defect zones (46.4±8) compared to regions with normal Tl-201 uptake (57.0±6;$p<0.01$). In 13 pts with exercise-induced transient Tl-201 defects who were paced to angina, average RMBF during pacing was consistently lower in zones of Tl-201 defects (64.2±18) than in zones with normal Tl-201 uptake (82.4±20; $p<0.001$). The mean difference between the normal and ischemic zones was 22%. Thus, 1) Tl-201 images are normal over a wide range of global LV flows if RMBF is homogeneous; 2) Tl-201 perfusion defects coincide with regional differences of myocardial flow averaging 22%.

SERIAL RIGHT VENTRICULAR THALLIUM IMAGING FOLLOWING DIPYRIDAMOLE AND RELATIONSHIP TO RIGHT CORONARY ARTERY DISEASE

Kenneth A. Brown, MD; Charles A. Boucher, MD, FACC; Robert D. Okada, MD, FACC ; Jeffrey Leppo, MD, Gerald M. Pohost, MD, FACC, H.William Strauss, MD, FACC, Massachusetts General Hospital, Boston, MA.

The right ventricle (RV) is frequently well defined on thallium imaging following dipyridamole. The relationship of RV thallium distribution to right coronary artery anatomy and left ventricular (LV) inferior wall thallium distribution was examined in 67 patients following dipyridamole. The RV and inferior LV wall were read on 10 minute and 2-3 hour delayed views in left anterior oblique and anterior position, and were interpreted as normal, or showing persistent defect (PD) or transient defect (TD).

The RV image showed TD in 18 patients; 18/18 (100%) had $\geq$50% stenosis of proximal or mid right coronary artery (P/M RCA), although inferior wall was normal in 9/18. Twenty-nine patients had both normal RV and inferior wall images; 27/29 (93%) had no P/M RCA disease. When the RV showed PD, the inferior wall segment was predictive: 4/4 patients with inferior wall defect had P/M RCA disease, while 6/6 with normal inferior wall did not. However, when RV showed normal distribution, only 3/5 patients with inferior wall TD and 2/5 with inferior wall PD had P/M RCA disease.

The sensitivity/specificity was then examined. Of the 67 patients,30 had P/M RCA disease, 4 had disease of RCA limited to distal portion and 34 had normal RCA. For P/M RCA disease, the sensitivity of RV imaging (PD+TD) was 77% and was 60% for inferior wall defect (PD+TD)(P=NS). Combined RV plus inferior wall sensitivity was 93%, which was significantly higher than either alone ($P<.05$). For distal RCA disease, the sensitivity of both RV and inferior wall imaging was 1/4. The specificity of RV was 84%, of inferior wall 87%, of combined RV plus inferior wall 71%.

Thus, with serial thallium imaging following dipyridamole: 1) RV transient defect is highly specific for P/M RCA disease, 2) the combinaton of normal RV and inferior wall distribution is highly predictive for absence of P/M RCA disease, 3) inferior wall defects were predictive of P/M RCA disease only when RV showed PD, 4) for P/M RCA disease, the evaluation of both RV and inferior wall distribution defects adds significantly to the sensitivity of either RV or inferior wall defects alone.

PREDICTING THE EXTENT AND LOCATION OF CORONARY DISEASE TWO-WEEKS POST-MYOCARDIAL INFARCTION BY THALLIUM-201 SCINTIGRAPHY

Robert S. Gibson, MD; George J. Taylor, MD; Denny D. Watson, PhD; Richard C. Crampton, MD, FACC; George A. Beller, MD, FACC, University of Virginia, Charlottesville, Va.

The ability of quantitative thallium-201 (Tl) scintigraphy to predict the extent and location of coronary artery disease (CAD) prior to discharge after acute infarction (MI) was evaluated in 65 consecutive patients (pts). All pts underwent coronary angiography (CA) and serial Tl imaging either at rest (12 pts) or following submaximal exercise stress (53 pts; target heart rate 120). Two or 3 vessel CAD was designated if abnormal Tl uptake and/or washout patterns were seen in 2 or 3 vascular scan segments, respectively. Of 181 vessels analyzed in the 65 pts, 116 stenoses (STEN) $\geq$ 70% were found by CA. Ninety-four of these (81%) were predicted by scintigraphy. The specificity for identifying vessel STEN was 91%. Sensitivity for detecting and localizing STEN supplying an infarct zone was 95% as compared to 63% for STEN perfusing myocardium remote from the acute infarct ($p<0.002$). Perfusion abnormalities were more frequently seen in the distribution of vessels with severe ($\geq$90%) STEN than in those with moderate (70-90%) STEN (86% versus 56%, $p<0.02$). A greater proportion of LAD and RCA STEN (90%, 38/42 and 89%, 31/35, respectively) were detected by scintigraphy than Cx STEN (64%, 25/39)($p<0.006$). In 26/35 (74%) pts with 2 or 3 STEN by CA, scintigraphy predicted multivessel CAD.

Thus, 2 weeks after MI Tl scintigraphy is useful for predicting the extent and location of CAD, particularly STEN in the LAD and RCA. Low level stress or rest imaging is highly sensitive for detection of $\geq$ 90% STEN but less so for 70-89% STEN.

THURSDAY, MARCH 19, 1981
AM
SURGERY FOR CORONARY ARTERY DISEASE—I
8:30-10:00

RESULTS OF CORONARY BYPASS AT LEAST 10 YEARS AFTER OPERATION IN 250 PATIENTS

Gerald M. Lawrie, MD, FACC; George C. Morris, Jr,MD,FACC; Abraham Silvers, PhD; Don W. Chapman, MD, FACC; Baylor College of Medicine, Houston, Tex.

The aim of this study was to determine the outcome of coronary bypass operation in 250 patients (pts) operated upon between 1968 and 1971 and followed in all cases for at least 10 years. There were 224 males (89.4%). Mean age at operation was 51.2 years. One vessel (V) disease was present in 23.3% (58) pts, two V in 44.4% (111) pts, three V in 26.5% (66) pts, and left main (> 50%) in 6.0% (15) pts. Good left ventricular (LV) function was present in 66% (165) pts and poor in the remainder. Operation was for angina pectoris in 96.3% (241) pts. Follow-up obtained for 96.4% (241/250) pts. Perioperative mortality was 6.8% (17 pts). Survival at 10 years was for one V, overall 77% (45 pts); good LV 80% (40 pts); poor LV 70% (5 pts); two V overall 69%, (76 pts); good LV 78% (48 pts); poor LV 58% (28 pts); three V overall, 51% (35 pts); good LV 56% (23 pts); poor LV, 50% (12 pts); left main overall, 60% (9 pts). Graft patency between 5 and 10 years (mean 8.4 years) was 77.4% (257/332). Of 165 survivors, 58% (96) were asymptomatic, 26% (43) improved, while 16% (26) felt unchanged or worse. Of patients under 65 at followup, 76% were employed fulltime and 19% were not working. Cox multivariate analysis showed factors most predictive of 10 year survival were age at operation, preoperative LV function and the number of vessels diseased preoperatively. The favorable 10 year results obtained in this early group suggests that long-term relief of symptoms and good late survival can be obtained with coronary bypass. The fact that late annual attrition rates have remained stable is particularly encouraging.

BYPASS GRAFT SURGERY FOR CORONARY ARTERY DISEASE: A 10-13 YEAR FOLLOW-UP STUDY OF 741 PATIENTS

William C. Sheldon, MD, FACC; Gustavo Rincon, MD, FACC; Floyd D. Loop, MD, FACC; William L. Proudfit, MD, Cleveland Clinic Foundation, Cleveland, OH

Seven hundred forty-one consecutive patients (pts.) had coronary artery vein graft surgery between May 1967 and December 1970, including 632 men and 109 women, median age 50 yrs. Single-vessel disease (lesions > 75% except for 21 pts.) was present in 414 pts. (55.9%), double-vessel disease in 195 (26.3%), triple-vessel disease in 69 (9.3%), and left main disease in 63 (8.5%). Twenty-two pts. died in the hospital (3%). All but 2 were followed 114-159 mos. after surgery. Ninety-seven required repeat cardiac operations 1-136 mos. after operation. One hundred thirty-two pts. died 2-135 mos. after hospital discharge (at least 37 of noncardiac causes). Five and 10-year survival for the entire series was 89.4% and 77.3%, respectively. For subsets with single-vessel involvement, 5 and 10-year survival rates were 91.5% and 81.3%, respectively; double-vessel involvement 87.8% and 75.9%. triple-vessel involvement 84.8% and 62.3%, and left main disease 85.5% and 72.9%. In the absence of a control series of matched or randomized medically treated pts., only the Proudfit series of angiographically documented surgical candidates (1963-1965) is available for comparative purposes: 5- and 10- year survival for the composite series of 388 surgical candidates was 70.1% and 47.9%, respectively. For subsets with single-vessel disease, 5 and 10-year survival was 88.3% and 68.4%, respectively, double-vessel disease 68.5% and 51.4%, triple-vessel disease 56.5% and 29.5%, and left main disease 55.6% and 25.7%. It is suggested that surgical treatment has a favorable benefit on long-term survival for all subsets of pts.

FACTORS INFLUENCING RESULTS DURING 12 YEARS OF CORONARY ARTERY BYPASS SURGERY IN 7,362 PATIENTS.

Jack C. Manley, MD., FACC; James F. King, MD; Jacob Assa, St. Luke's Hospital, Milwaukee, Wisconsin.

Using a computerized data registry system, analysis was made of factors influencing surgical results during two time periods; early (1968-71) and late (1972-79). Surgery was performed at one hospital by 4 senior surgeons with similar degree of experience and basic approach. Surgical mortality in the early time period in 1,085 patients ranged from 16 to 6% normal left ventricle (N-LV) 6.1%, abnormal LV (ABN-LV) 12.7%. Surgical mortality in the later time period in 6,277 patients ranged from 3 to 1.8%. (NLV-1.4% and ABN-LV 2.6%). During those observation times, median age increased (I) from 51 to 54 years, frequency of multivessel disease I 71 to 78%, severity of ABN-LV decreased 60.9% to 46.2%, average number of grafts per patient I 2.3 to 3.6, early graft patency (average 15 days) I 86.2 to 94.4%, late graft patency (60 months) I 78-86%. Number of mammary grafts I from 66 to 5,922 with average overall patency consistently over 94%; complication rates during later time period decreased in all catagories except neurologic deficit; perioperative infarction rates decreased 6.1 to 2.5%; 8 year actuarial survival in early time period was 70.1% (N-LV 81.0%,ABN-LV 62.3%) with annual attrition rates of 3.75, 2.37, 4.75% respectively. In later time periods 8 year survival increased to 89.1% (N-LV 91.2%,ABN-LV 88.2%) with annual attrition rate of 1.37, 1.1 and 1.47% respectively. Lower risk of surgery survival is attributed to greater technical experience, expertise and technology, more complete revascularization with greater graft patency, better patient selection and management. Most recent patient cohort (1978-80) demonstrates further improvement of surgical mortality, complication rates, graft patency and survival.

TEN YEAR EXPERIENCE WITH THE INTERNAL MAMMARY ARTERY AS A CORONARY BYPASS GRAFT

Jack C. Manley, MD, FACC; James F. King, MD; Jacob Assa; St. Luke's Hospital, Milwaukee, Wis.

The internal mammary artery (IMA) has not gained wide acceptance as a coronary bypass conduit, in part because of doubt regarding its ability to provide adequate perfusion and because of the extra effort involved in mobilizing the IMA from the chest wall. Because of our own increasing experience and reliance on the IMA bypass graft (BG), we reviewed the results at one hospital of 4 senior surgeons between 1970 and 1980. These surgeons who have similar experience and basic approach began to use the IMA in 1970-71 (66 IMA BG). Since that initial experience, 5,922 IMA BG have been placed in 6,277 patients. Surgical mortality, complication rate, postoperative exercise stress test, exercise hemodynamics at catheterization, relief of angina, and 8 year survival rates are comparable between patients with both vein G and IMA. In patients undergoing postoperative catheterization and angiography because of angina after surgery, vein G patency to anterior descending, diagonal and marginal branches was 73% (720 G) whereas IMA patency in the same patients to similar vessels was 94% (420 G). Angiography from 1-8 years (average 60 months) revealed a larger size of IMA, rare atherosclerosis and continued high patency rates (> 92%). Similar palliation and clinical results were observed in patients with single IMA and single saphenous vein revascularization. The findings support experimental studies that indicate adequate myocardial perfusion with IMA BG. In view of higher patency rates, this conduit is preferable alone or in combination with saphenous vein BG.

EFFECT OF MEDICAL AND SURGICAL THERAPY ON PROGNOSIS IN PATIENTS WITH ISOLATED LEFT ANTERIOR DESCENDING CORONARY ARTERY DISEASE

Ezra A. Amsterdam, MD, FACC; Todd M. Grehl, MD, FACC; Garrett Lee, MD; James A. Joye, MD, FACC; Reginald I. Low, MD; Asher Kimchi, MD; Esther Tow; Edward J. Hurley, MD, FACC; Anthony N. DeMaria, MD, FACC; Dean T. Mason, MD, FACC, University of California, Davis, California.

The effect of coronary artery bypass graft surgery on prognosis in patients (pts) with isolated disease of the left anterior descending coronary artery (LAD) has not been clarified. Therefore, follow-up data were analyzed in 74 pts with isolated stenosis ($\geq$ 70%) of the LAD treated medically (Med, 51 pts) and by coronary artery bypass graft surgery (Surg, 23 pts) during the past 9 yrs. Duration of follow-up was 31 mos in Med and 46 mos in Surg pts. There were no significant differences ($P > .05$) between Med and Surg pts, respectively, in age (53 vs 53 yrs), sex distribution (males 42/51, 82% vs 16/23, 70%) or left ventricular (LV) ejection fraction (0.64 vs 0.69; $>$ 0.40 in all 74 pts). Prevalence of prior myocardial infarction (MI) was higher ($P < .05$) in Med than Surg pts (32/51, 63% vs 9/23, 39%). Mortality during the period of observation in Med pts was 7.8% (4/5, 3.0%/yr): 1 death in 20 pts without prior MI (1.9%/yr) and 3 deaths in 32 pts with prior MI (3.6%/yr); there was no mortality (0/23) in Surg pts. New MI was comparable in Med and Surg pts: Med pts - 6 (4.6%/yr) and Surg pts - 3 (3.4%/yr). Mortality in pts with isolated disease of the left anterior descending coronary artery associated with adequate LV function and no prior MI is low with both Med and Surg therapy but is increased in Med pts with prior MI.

UNSTABLE ANGINA: EFFECT OF MEDICAL VERSUS SURGICAL THERAPY ON SURVIVAL AND MYOCARDIAL INFARCTION.

Herbert N. Hultgren, MD, FACC; Udipi Shettigar, MD, FACC; Craig Miller, MD, FACC. VA Medical Center, Palo Alto, California.

A prospective, non-randomized data bank study of the effect of medical versus surgical management of patients with unstable angina included all patients with unstable angina seen at one hospital over an 8 year period. Patients were entered into the study after an initial 5 day period of medical treatment. Entry characteristics were similar in 104 surgical patients and 124 medical patients. The mean follow-up period was 40 months. Operative mortality was 2% (2/104). The incidence of operative infarction was 13% (13/104). Twenty-seven medical patients had late surgery for progressive angina without operative mortality. Results are summarized below for 5 year survival by initial treatment (S_1%), by treatment received (S_2%) and by crossover where medical patients are dropped when surgery is performed (S_3%). Cardiac deaths only are considered. Operative infarcts (OMI%) and total infarcts (TMI%) are shown:

	No.	S_1%	S_2%	S_3%	OMI%	TMI%
Med.	124	.75*	73%**	76*	0%	17%
Surg.	104	.91	91%	91%	13%	22%

* p = <.025 ** p = <.01

Non-survivors compared to survivors had a higher incidence of: 1) Age >60 yrs; 2) Diastolic BP >89 mm; 3) ST-T changes; 4) Three vessel disease; 5) Elevated LV diastolic pressure (rest); 6) Elevated LV diastolic pressure (exercise). None had single vessel disease. Surgical therapy in this high risk study group improved survival but total infarcts were not reduced due to the incidence of operative infarction.

THURSDAY, MARCH 19, 1981
AM
LONG TERM PROGNOSIS IN CARDIOVASCULAR DISEASE
8:30-10:00

CLINICAL IMPLICATIONS OF SERUM DIGOXIN CONCENTRATIONS

H.R. Ochs, MD; D.J. Greenblatt, MD; J.S. Harmatz; G. Bodem, MD; H.J. Dengler, MD, Med. Univ.-Klin., Bonn, W. Germany, and Tufts-New England Medical Center, Boston.

Factors influencing serum digoxin concentrations (SDC), and the relation of these levels to classical ECG and clinical manifestations of toxicity, were assessed in a series of 463 consecutively hospitalized patients of mean age 58 years. ECG variables were assessed by a blind observer who had no knowledge of SDC or patients' clinical status. Patients completed a standardized questionnaire assessing the presence or absence of subjective symptoms usually associated with digitalis toxicity; these were also scored by a blind observer. The majority of patients were receiving beta-acetyldigoxin (n=212) or beta-methyldigoxin (n=136). Age, sex, creatinine clearance, and weight-corrected dose collectively explained less than 7% of overall variability in SDC. Creatinine clearance, which declined significantly with age ($r=-.36$, $p<.001$), was the most important of these determinants. ST-segment depression was present in the majority of patients and became more common at higher SDC (Chi-square=22.6, $p<.01$). However, PR interval, QRS duration, QT interval, or the presence of AV block were not associated with SDC. Among 75 patients with atrial fibrillation, ventricular rate did not decline with increasing SDC, but was in fact positively correlated with SDC ($r=.20$). The presence of gastrointestinal, neuromuscular, or psychiatric symptoms classically attributed to digitalis toxicity was not significantly associated with SDC. SDC appear to be of limited value in assessing ECG and subjective manifestations usually associated with digitalis toxicity.

HIGH DENSITY LIPOPROTEIN AND TOTAL CHOLESTEROL AS PREDICTORS OF 7-YEAR MORTALITY FROM CORONARY HEART DISEASE, CANCER AND ALL CAUSES

Uri Goldbourt, MA; Shlomit Yaari, BA; Henry N. Neufeld, MD, FACC, Sheba Medical Center, Tel Hashomer, Israel.

10059 adult civil servants and municipal employees aged 40-65, were examined in the Israeli Ischemic Heart Disease Study. 475 (4.72%) died during a 7-year follow-up. For the 6562 last examinees, high density lipoprotein cholesterol (HDL) levels were determined. 305 of these died (4.65%). A J-shaped relationship which persisted after removing the early mortality (first two years) was observed between total cholesterol (CHOL) and total mortality (age adjusted mortality rates in the first through fifth CHOL quintiles: 44, 40, 39, 46, and 63 per 1000, respectively). An inverse relationship was observed between HDL and total mortality, the corresponding rates being: 63, 44, 39, 44 and 36 per 1000. In a multivariate logistic regression (MLR) the association with CHOL vanishes while that with HDL is augmented (adjusted relative odds, associated with decrease of one standard deviation = 1.21, $p < .005$). Coronary heart disease mortality is related dose response to both CHOL and (inversely) HDL, the latter relationship emerging the dominant one after adjustment for age and 8 other risk factors in MLR. No clear cut association of CHOL or HDL to cancer mortality is observed. Even in the absence of previously suggested toxicity of very low cholesterol, it would appear a more prudent preventive policy to pursue the elevation of HDL cholesterol rather than the reduction of low density lipoprotein cholesterol, particularly at the older age span.

FAMILIAL HYPERCHOLESTEROLEMIC FAMILIES' RESPONSE TO FOOD PRODUCTS CONTAINING LBG

James H. Zavoral, MD; Donna Fields, RD; Madge Hansen, RD; Kanta Kuba, MS; Ivan Frantz, MD; David Jacobs, PhD, University of Minnesota, Minneapolis, Minnesota

Familial hypercholesterolemia (FHC) is associated with severe premature coronary artery disease, death, and is resistant to dietary treatment. A special diet was developed to evaluate the lipid-lowering effect of Locust Bean Gum (LBG) in food products fed to adults and children from families with familial hypercholesterolemia as a potential aid in preventing coronary artery disease. Twenty-eight adults and children (20 FHC, 8 N) were divided into two groups, using a crossover design, and fed food products with and without LBG (8-30 gm/d) as outpatients in four-week periods. Diet records, food product consumption, lipids, and lipoproteins were analyzed every two weeks. Total cholesterol was lowered 11% ($\bar{m}$ 275 to $\bar{m}$ 246) in Group A at four weeks and 16% ($\bar{m}$ 255 to $\bar{m}$ 215) in Group B at six weeks ($p < .01$). The difference in cholesterol between the LBG and control diet was 19% at four weeks ($p < .01$). Low-density lipoprotein (LDL) fell 10% at four weeks in Group A and 20% at six weeks in Group B. High-density lipoprotein (HDL) did not change. HDL/LDL ratios increased. Lipid lowering was proportionate to starting levels in FHC and N in adults and children. LBG food acceptance was good. There were no significant side effects of the diet. LBG was more effective than some pharmacological agents in lowering serum lipids, and, in outpatients, appears to be one of the most effective dietary treatments of FHC. LBG in food products appears to be a safe, effective means of lowering serum lipids in normal and hyperlipidemic members of FHC families.

PROGNOSIS OF MEN AFTER FIRST ACUTE MYOCARDIAL INFARCTION IN THE 1960's AND 1970's: SEARCH FOR A SECULAR TREND

Eve Weinblatt, AB; William Ruberman, MD, FACC; Judith D. Goldberg, ScD; Charles W. Frank, MD, FACC; Mary Monk, PhD Health Insurance Plan of Greater New York, New York City

A decline in coronary heart disease (CHD) mortality in the U.S. of about 20% took place between the late 1960's and the end of the 1970's. The extent to which this decline may reflect changes in cardiovascular risk factors (primary prevention) and/or improved medical care for coronary patients (secondary prevention) is unknown. The existence of data from two CHD prognosis studies among men enrolled in HIP in the 60's and 70's provided a unique opportunity to examine a specific issue: over this 10-year period was there any suggestion of improved long-term prognosis among men who had survived a first acute myocardial infarction (MI)?

Cohorts for this comparison consisted of men aged 35-64 who met identical study criteria for a first definite MI, had a baseline examination, and were followed for mortality for periods up to 4½ years thereafter. The 60's study provided 436 men and the 70's study 697 men for the new analyses. The 70's cohort was examined sooner after MI and had greater proportions with ST depression, angina, and failure than the 60's cohort. Improved hospital care for the acute MI's in the 70's might have resulted in the survival to baseline of a greater proportion of men with more advanced heart disease. But the subsequent prognosis showed no advantage for the 70's cohort even after adjusting for the differences in clinical and personal characteristics of prognostic importance. We conclude that any contribution of improved medical care to the secular decline in CHD mortality is probably restricted to the acute stage of myocardial infarction.

PREDICTIVE VALUE OF THE MINNESOTA CODE CRITERIA FOR ACUTE MYOCARDIAL INFARCTION: CORRELATION WITH TECHNETIUM 99m PYROPHOSPHATE SCINTIGRAPHY AND SERUM ENZYME EVALUATION

Marian C. Limacher, M.D., William H. Fennell, M.D., James B. Young, M.D., FACC, Nicholas Kutka, M.D., James K. Alexander, M.D., FACC, Richard R. Miller, M.D., FACC, Baylor College of Medicine, Houston, Texas.

Although the Minnesota Code electrocardiographic (ECG) criteria for documenting acute myocardial infarction (AMI) is the epidemiologic standard for national multicenter trials, validation by current sensitive indices of myocardial necrosis is incomplete. We determined the sensitivity and predictive accuracy of Minnesota Code Class using technetium 99m pyrophosphate (TcP) scans and serum cardiac enzyme (SE) confirmation of AMI. Minnesota Code criteria: I = presence of .04 sec Q waves; IV = J point and ST depression; V = T inversion; IX = J point and ST elevation. TcP scans were regarded as positive when uptake was well defined and either diffuse or localized (i.e., ≥2+). Scans were performed within 3.5 days (mean) of admission and interpreted in a blind fashion. Daily ECG and/or SE were abnormal in 104 consecutive patients undergoing TcP to diagnose AMI. Positive (+) SE = two cardiac enzymes ≥ twice normal.

MC Class (No.)	+SE and +TcP (%)	-SE and -TcP (%)	+SE and -TcP (%)	-SE and +TcP (%)
I (22)	14 (64)	4 (18)	4 (18)	0
IV (20)	2 (10)	10 (50)	8 (40)	0
V (50)	2 (4)	30 (60)	17 (34)	1 (2)

The predictive values of Minnesota Code for diagnosing acute myocardial infarction (+SE and +TcP) were I=78%, IV=16%, V=6%, IX=30%. Thus, 1) the predictive value of MC Class I is satisfactory; however, its sensitivity is only 64%; 2) criteria for non-transmural MI, though sensitive, are very non-specific.

COHORT ANALYSIS OF SECULAR CHANGE IN MORTALITY IN PATIENTS WITH CAD UNDERGOING SURGICAL INTERVENTION

A.Oberman; G.Cutter; N.Kouchoukos; W.Rogers; R.Russell; H.Cohen. The University of Alabama in Birmingham, Birmingham, Alabama.

In this paper we examine mortality trends on patients undergoing bypass surgery over the past 10 years at the UAB and VA hospitals in Birmingham. Three year survival rates have risen from under 88% to over 92% for those undergoing surgery from the early '70s to the late '70s. Cohort life table analyses by degree of stenosis and year of surgery show that for persons with >75% stenosis the actuarial one year survival rate has risen from 80% before 1970 to 93.3% in '71-'72; and 95.1% for '77-'78. Two year survival rates rose from 91.3% in '71-'72 to 93.9% in '73-'74 to 94.3% in '75-'76. Changes in the age adjusted death rates in the U.S. for major cardiovascular diseases declined from 350 per 10,000 in 1969 to 340 in 1970 and 335, 334, 327, 311, 291, 284 for 1971-76 respectively. The gains in patients' survival appear to be greatest between the '71-'72 cohort versus the '73-'74 cohort. The lack of similar changes in the relative survival rates suggest real improvement in surgical management as opposed to simply secular trends in mortality. Similar changes and shifts between '71-'72 and '73-'74 were found for patients with 50-75% stenosis. These secular changes are not explained by differences in severity of disease, age, and sex in the patients undergoing surgical intervention.

THURSDAY, MARCH 19, 1981
AM
THE VENTRICLES III: MAPPING
8:30-10:00

NON-COMPUTERIZED ON-LINE EPICARDIAL AND INTRAMURAL MAPPING OF VENTRICULAR ARRHYTHMIAS.
Eugene Downar, MD; Ian Parson, PhD; Paul Mendler, Dept. of Medicine, University of Toronto, Toronto, Canada;

In 6 in-situ canine hearts, local electrograms (LE) from 112 transmural multipolar needle electrodes were recorded on video tape by a multiplexing technique. The electrode positions were displayed in a polar projection of the heart on a video screen. Activation at each site was monitored continuously by differentiation of the dominant negative deflection of the LE and indicated by light intensification of the video display. Recording this data in video format enabled instant playback to be made one frame at a time. Each frame showed activation at 8 msec intervals. Ventricular pacing from the electrode sites demonstrated localization of the point of origin to within one centimeter. Subepicardial mapping was displayed by selecting a deeper electrode on all needles. Coronary occlusion produced a defect in the displayed image which was maximal at 7 mins but was markedly reduced by 15 mins. Ventricular ectopics and runs of ventricular tachycardia emerged from within the ischemic border. Reperfusion produced ventricular fibrillation by disintergration of the activation sequence within 1 or 2 cycles as well as by acceleration of monofocal tachycardias originating in the subendocardium. Multiplexing and video techniques offer an effective means of mapping myocardial activation.

CONFIRMATION OF A NEW TECHNIQUE FOR DETECTING SLOW VENTRICULAR ACTIVATION ON THE BODY SURFACE
Michael B. Simson, MD, FACC, David E. Euler, PhD, Eric L. Michelson, MD, FACC, Rita Falcone, BS, Joseph F. Spear, PhD, FACC, E. Neil Moore, DVM, PhD, FACC, University of Pennsylvania, Philadelphia, PA.

We tested the hypothesis that slow, fractionated ventricular activation after myocardial infarction (MI) can be detected on the body surface using a computer processed ECG in 19 dogs. Bipolar XYZ leads were signal averaged (SA) and processed with a bi-directional, 60 Hz high-pass, digital filter. During sinus rhythm, epicardial, transmural and endocardial mapping was performed to identify areas of delayed activation. After each map the chest was closed and a 300 beat SA performed. Eight animals were studied prior to and up to 100 minutes after MI. Before MI, the QRS duration by SA was 60 $\pm$ 5 msec (mean $\pm$ SD). After acute MI, all dogs had fractionated electrograms lasting 119 $\pm$ 13 msec after QRS onset. The maximum delay was from epicardial sites. In all cases, SA detected a low amplitude tail of high frequency energy at the end of the QRS, with a peak amplitude of 2.4 $\pm$ 2.0 μV, lasting 61 $\pm$ 17 msec, and ending 115 $\pm$ 13 msec after QRS onset. The duration of the fractionated activity varied with time. There was a good correlation (r=0.91, 34 pairs) between total ventricular activation time and total SA signal duration. Fractionated electrograms were detected on the body surface which arose from epicardial areas as small as 1 cm^2. In 11 other dogs, studied 3 hrs to 5 days after MI, fractionated activity was seen in 3 and detected on the body surface of those dogs. No evidence of slow ventricular activation was seen in the other 8 dogs, either by ventricular mapping or by SA.

Conclusion: With advanced signal processing, slow ventricular activation after myocardial infarction can be reliably detected on the body surface.

ENDOCARDIAL PACE-MAPPING TO LOCALIZE THE ORIGIN OF VENTRICULAR TACHYCARDIA
Mark E. Josephson, MD, FACC; Harvey L. Waxman, MD; Michael E. Cain, MD; Leonard N. Horowitz, MD, FACC; John A. Kastor, MD, FACC, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Intraoperative epicardial pace-mapping (PM) has been proposed as a method of identifying the origin of ventricular tachycardia (VT); however, limitations of both epicardial activation and ECG morphology in localizing VT origin have been demonstrated. Since most VT associated with ischemic heart disease appear to arise near the endocardium, we evaluated the ability of bipolar catheter endocardial pacing (1 cm interelectrode distance) at or near the endocardial site of origin of VT to mimic QRS morphology and/or ventricular activation pattern of VT. We studied 10 patients (pts) with VT in whom the origin was determined by catheter endocardial mapping and in 6/10 confirmed at surgery. One pt had VT with two distinct morphologies. The 12 lead ECG of VT was compared to the 12 lead ECG produced by pacing the site of origin (8 pts) and multiple other sites in five pts. In the remaining two pts, limited ECG leads and activation times to one or two ventricular reference electrograms during VT were compared to those recorded during pacing the site of origin. We observed that: 1) pacing the known site of VT origin produces a similar ECG and activation sequence as VT; 2) the ECG of VT could not predict the origin; 3) pacing from sites in close proximity to site of VT origin could produce either a similar or a grossly different ECG pattern than during VT. We conclude that catheter endocardial PM: 1) is a corroborative method of identifying VT origin, and 2) may be useful in pts with non-inducible VT or rapid VT who cannot undergo catheter or intraoperative mapping.

ESTIMATION OF VENTRICULAR TRANSMEMBRANE ACTION POTENTIAL DURATIONS AND REPOLARIZATION TIMES FROM UNIPOLAR ELECTROGRAMS
R.F. Wyatt, B.S.; M.J. Burgess, M.D.; A.K. Evans, Ph.D.; R.L. Lux, Ph.D.; J.A. Abildskov, M.D., F.A.C.C. and T. Tsutsumi, M.D.; University of Utah, Salt Lake City, Ut.

A method for estimating ventricular transmembrane action potential (TMAP) durations, depolarization times (T_D) and repolarization times (T_R) from unipolar electrograms (UE) was developed. The method was based on assumptions that minimum derivative of the QRS and maximum derivative of the T in UE correspond to T_D and T_R respectively, and that TMAP duration equals the interval between T_D and T_R. To test these assumptions, UE, bipolar electrograms (BE), and in vivo TMAPs were recorded in 8 dogs during paced cycle lengths (CL) of 300 to 650 ms stepped in 50 ms increments, during coronary occlusion (CO) and release (CR), and during epinephrine infusion (EI). Refractory periods (RP) were measured with extrastimuli during changes in CL. Data were pooled. Correlation coefficients (r) and standard error of estimates (SEE) between TMAP durations measured from in vivo recordings and those estimated from UE, BE and RP are shown below. SEE is given in ms.

	UE		BE		RP	
Intervention	r	SEE	r	SEE	r	SEE
CL	.83	11	.77	13	.55	34
CO	.89	15	.76	26	-	-
CR	.92	11	.90	13	-	-
EI	.89	26	.75	31	-	-
all	.85	16	.77	21	.55	34

The high correlation between estimates of TMAP duration from UE and measurements from in vivo TMAP recordings indicates UE can be used to study TMAP duration at multiple sites and during rapidly changing states in the intact heart.

ENDOCARDIAL MAPPING OF TRIGGERED AUTOMATICITY IN CANINE ISCHEMIC PURKINJE FIBERS

Nabil El-Sherif, MD, FACC; William B. Gough, PhD; Robert Zeiler, MS, Rahul Mehra, PhD, Downstate and VA Medical Centers, Brooklyn, N.Y.

Ventricular arrhythmias seen 24 hours following myocardial infarction (MI) in dogs have been recently shown to be due to triggered automaticity (TA) in ischemic depolarized Purkinje fibers (PF) (El-Sherif et al, Circulation, In press). Utilizing a standard microelectrode technique and endocardial preparations from 24-hour-old MI in dogs TA automaticity arose from a delayed after-depolarization (DAD) and TA stopped when a DAD failed to reach threshold. In quiescent preparations TA was consistently induced by a critical cycle length during regular pacing or premature stimulation and only when DAD attained threshold. To further identify the mechanism of TA we analyzed endocardial activation patterns utilizing a 16-electrode grid with an interelectrode distance of 1-2mm and a multiplexer recording system. Simultaneous recordings of extracellular unipolar electrograms were obtained and isochronic activation maps were constructed. When stimulation of a normal endocardial site initiated TA, the latter was localized to ischemic endocardium. Critical analysis of endocardial activation pattern of the stimulated beat that initiated TA failed to show evidence of reentrant activation. In some preparations background slow automaticity was able to initiate faster TA. Analysis of isochronic maps showed that sudden acceleration of rate was associated with shift of the pacemaker site with the fast TA arising from ischemic endocardium. We conclude that TA in ischemic PF and not reentrant activation is the common mechanism of ventricular arrhythmias seen in dogs 24 hours following MI.

THURSDAY, MARCH 19, 1981
AM
DRUG INTERVENTION IN ACUTE MYOCARDIAL ISCHEMIA
8:30-10:00

PAIN RELIEF IN ACUTE MYOCARDIAL INFARCTION BY INTRAVENOUS ATENOLOL

David R. Ramsdale, MRCP; Eric B. Faragher, FSS; David H. Bennett, MRCP; Colin L. Bray, FRCP; Christopher Ward, MRCP; Salim Yusuf, MBBS; Peter Sleight, FRCP, The Regional Cardiac Centre, Wythenshawe Hospital, Manchester, U.K.

The cardioselective beta-blocker atenolol (AT) was given intravenously (IV) in a double-blind study to assess pain relief after acute myocardial infarction (AMI). Eighteen patients were randomly allocated to treatment with 5mg AT (0.5mg/ml) or 10mls 0.9% saline intravenously immediately after admission, followed by 50mg AT or matching placebo orally 10 mins later. Heart rate (HR), blood pressure (BP) and "pain score" were recorded before and at intervals after injection. These parameters were unchanged by IV saline but were significantly reduced after IV AT as shown below. (Values are mean ± SD)

	Pre.AT	1hr.post AT	p value
HR (bpm)	67±9	58±12	< 0.05
HR x syst. BP (bpm x mmHg)	9350±1010	6620±1670	< 0.05
Pain score	2.60±1.00	0.50±0.40	< 0.01

These results were supported by an open study of 22 patients with AMI receiving IV (5-15mg) AT plus 50mg AT orally during the first hour after admission. Seventeen patients obtained pain relief together with reduction in HR and BP, in contrast to the five remaining patients who did not achieve any reduction in these parameters.

CONCLUSIONS. Patients with AMI can obtain pain relief with IV AT given immediately after admission and this is usually related to achieving a reduction in HR and BP.

ESTIMATION OF VENTRICULAR REPOLARIZATION DURATION AND DISPARITY FROM DISTRIBUTIONS OF QRST AREA

R.L. Lux PhD; J.A. Abildskov, MD, FACC; R.F. Wyatt, BS; A. Kerry Evans, PhD; M.J. Burgess, MD. University of Utah, Salt Lake City, Utah

Disparity of ventricular repolarization contributes to ventricular arrhythmia vulnerability and is also a major factor in determining QRST deflection area (AQRST). Previous evidence that arrhythmia prone states can be identified by AQRST distributions has not included direct documentation of disparate repolarization. Although AQRST has been shown to be a measure of the gradient of recovery properties, no relation to absolute repolarization duration (RD) has been established. New evidence using direct RD measurements suggests use of cycle (CL) might permit practical estimates of RD and its disparity. RD and AQRST were determined from 75 unipolar, epicardial electrograms in each of 6 open-chest dogs, for up to 4 different activation orders and 4 to 6 CL with range 300-900 ms. RD was measured from times of minimum derivative in QRS to maximum derivative in T which we have shown correlates with transmembrane action potential duration. AQRST was calculated by integrating each electrogram over the QT interval. Mean and variance of RD increased with increasing CL confirming prolongation and increased disparity at slow rates. Mean and variance of AQRST also increased with CL in electrograms as well as 192 body surface leads recorded during the same pacing modes prior to thoracotomy. At each CL, RD and AQRST were negatively correlated [-.8<r<-.4] with standard errors of 4-8 ms across all activation orders. RD range was 140-290 ms. Findings suggest AQRST distributions from extensively sampled electrograms can provide practical estimates of RD as well as its disparity. The clinical implication is that measured AQRST distributions may be used to estimate CL corrected values of RD and its disparity.

THE EFFECTS OF NITROGLYCERIN ON INTRACORONARY PLATELET AGGREGATION AND VENTRICULAR VULNERABILITY DURING PARTIAL CORONARY STENOSIS

Peter R. Kowey, MD; Richard L. Verrier, PhD, FACC; Bernard Lown, MD, FACC, Robert I. Handin, MD. Cardiovascular laboratories, Harvard School of Public Health, and Harvard Medical School, Boston, Mass.

Partial coronary stenosis (PCS) has been shown to cause phasic myocardial ischemia and enhanced vulnerability to ventricular fibrillation. The objectives of this study were to determine whether nitroglycerin (NTG) afforded protection during PCS and to delineate the mechanism for the observed protective effects. We induced PCS of the left circumflex vessel in 10 chloralose-anesthetized dogs, utilizing an externally applied plastic cylinder. Seven of these animals manifested spontaneous cyclical reductions in coronary blood flow (CBF) of from 30 to 80% (mean 55%). These reductions in CBF were accompanied by a decline in the ventricular fibrillation threshold (VFT) (43 ± 3 to 21 ± 3 ma, $p < 0.001$). Infusion of NTG (80 µg/min) caused a fall in mean arterial blood pressure of 15 ± 4 mmHg. Within 5 minutes of the start of the infusion, cyclical flow changes ceased and VFT returned to control values. NTG decreased ADP-mediated platelet aggregation from 46 ± 4 to 23 ± 2 Born units ($p < 0.01$) and prevented the occurrence of irreversible platelet aggregation. Administration of the antiplatelet agent, indomethacin (5 mg/kg), caused similar resolution of changes in vulnerability induced by cyclical changes in CBF. We conclude that NTG prevents myocardial ischemia and enhancement of vulnerability during partial coronary stenosis. These effects may be related to the drug's antiplatelet action.

FREQUENCY OF PROVOKED CORONARY ARTERIAL SPASM IN PATIENTS WITH RECENT TRANSMURAL MYOCARDIAL INFARCTION

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Provocative test with methergine(M) was performed in a group of 88 patients (pts)(82 men & 6 women)with recent (<6 weeks)transmural myocardial infarction(MI)who underwent coronary arteriography for evaluation of vessel disease.The diagnosis of MI was established by typical chest pain ,appearanceof new Q waves and increase in serum creatine kinase toa level above normal limits. 58 pts or 66% had anterior infarction,28 (32%)had inferior infarction and 2 lateral infarct.Coronary arteriography was performed 26±9 (m±SD) days after the onset of infarc--tion(range6 to 45).37 or 42% had 1 vessel disease (VD), 25 (28%)had 2 VD,19 or 22% had 3 VD whilst 7 had minimal but insignificant lesions.The provocative test was perfor med after the routine procedure of coronary arteriography using a protocol with a single bolus injection of 0.4 mg of methergine.Aortic pressure ,EKG and coronary arteriograms of the 2 vessels (left and right coronary artery) were repeated 3 and 5 minutes later.
Provoked coronary arterial spasm was observed in 18 or 20.5% of patients.9 patients or 10.25% had spasm superimposed on narrowings located on the vessel responsible of the infarction.In these cases spasm was not accompanied by pain or EKG changes.Nine other patients (10.25%)had provoked coronary arterial spasm located on a vessel which was not responsible of the infarction.In this group spasm was accompanied by pain and EKG changes.
Conclusion:1-Provoked coronary arterial spasm can be induced in 20 % of pts with recent MI .2-The vessel with the narrowing responsible for the infarction remains sensitive to methergine in 10% of cases.3-In 10% of cases spasm can be induced in vessel unrelated to MI.

NIFEDIPINE THERAPY FOR RECURRENT ISCHEMIC PAIN FOLLOWING ACUTE MYOCARDIAL INFARCTION

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Following acute myocardial infarction (MI) patients often experience recurrent episodes of ischemic pain at rest which may be due to coronary vasospasm. In order to determine the efficacy of nifedipine, a potent coronary vasodilator, in relieving rest ischemia, we administered nifedipine to 9 patients (pts) with recurrent rest pain a mean of 9.2 days post MI (range 2-42 days). Prior to MI, all of the pts had a history of exertional angina only, yet following the MI episodes of recurrent ischemia occurred at rest (mean # daily episodes 2.4, range 2-6) in spite of maximal medical management with β-blockers and/or nitrate preparations. Six of the 9 pts had a subendocardial MI, 3 had a transmural MI. Ischemic episodes were associated with ST-segment (ST) deviations in the same leads that displayed the acute MI pattern: 5 pts had ST elevation, 4 pts had ST depression or T inversion. Coronary angiography in 6 pts demonstrated multivessel coronary disease. In all pts the episodes of rest ischemia ceased following the initiation of nifedipine (mean daily dose 60 mg, range 40-120 mg). Two pts continued to have myocardial ischemia with minimal exertion and underwent coronary bypass surgery for pain relief. The other 7 pts have been managed medically for a mean of 5.4 months (range 1-12 months) and have remained pain free on combined regimens of nifedipine, β-blockers, and/or nitrate preparations. We conclude that nifedipine may be efficacious for the relief of recurrent myocardial ischemia at rest following acute infarction. In some pts nifedipine may eliminate the need for coronary artery bypass surgery and in others it may provide clinical stability prior to operation.

IMPORTANCE OF EARLY ADMINISTRATION OF INTRAVENOUS NITROGLYCERIN TO PRESERVE ISCHEMIC MYOCARDIUM

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Intravenous nitroglycerin (IV TNG) improves hemodynamics and regional ischemia in patients (pts) with acute myocardial infarction (AMI). In a prospective randomized trial, 48 hr infusion of IV TNG or Placebo (PLAC) was begun within 18 hr of onset of AMI in 104 pts to determine whether a prolonged infusion could preserve ischemic myocardium. IV TNG was titrated to lower mean arterial pressure 10%. Time between onset of pain and initiation of study drug (<or>10hr) defined early and late intervention. ^{201}Thallium perfusion scans and Tc^{99m} gated blood pool scans were performed on days 1 and 10. Thallium defects were scored by computer and were considered improved if a ≥ 2.5 unit reduction in score was obtained (range -11.0 to +5.6). Response of ejection fraction (EF) was considered good if EF remained ≥50% in pts with initial EF≥50% (31 pts) and good if EF increased ≥5% in pts with initial EF<50% (20 pts).

Defect Score	TNG<10 hr	TNG>10 hr	PLAC<10 hr	PLAC>10 hr
Improved	12	2	3	2
Not Improved	12	13	15	11
EF Response				
Good	17	9	7	4
Bad	1	4	6	3

Only in TNG <10 hr subgroup was there significant improvement in defect score (P=.032). Likewise for EF only in the TNG<10 hr subgroup was the beneficial effect significant (P=.056). These results demonstrate that early administration of IV TNG is important for improving myocardial perfusion and preserving function following AMI.

REDUCTION IN INFARCT SIZE AND MORBIDITY BY EARLY INTRAVENOUS BETABLOCKADE

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400 patients were studied in a randomised trial to determine whether administration of intravenous Atenolol (AT) (a cardioselective betablocker) within 12 hours of chest pain reduces eventual infarct size, morbidity and mortality. Infarct size and morbidity data (first 214 patients). 135 patients already had ECG evidence of infarction at entry: 72 received AT which significantly decreased subsequent cumulative MB-CPK release from 4-hourly measurements (intravenous AT and Control means = 121 I.U., SE ± 10 and 176 I.U., SE ± 17; $2p<0.005$) and enhanced R-wave preservation (mean R-wave score in AT and Control = 46% ± 3 and 36% ± 3; $2p < 0.02$). 79 patients had no evidence of infarction at entry; 44 did not receive AT and 27 of these subsequently developed infarction, whereas only 11 of the 35 treated patients infarcted during their hospital stay ($2p < 0.01$). In hospital fewer AT patients had non-fatal cardiac arrest (2 versus 6) or required therapy for heart failure in hospital (36 versus 47, $2p < 0.10$) or at discharge (19 versus 31, $2p < 0.05$). Mortality (400 patients): 14 AT patients and 24 Control patients have died since the start of the study ($2p < 0.10$). Conclusion: Intravenous Atenolol within 12 hours of pain prevents infarction in patients with initial threatened infarcts, and reduces infarct size and morbidity in Acute Myocardial Infarction.

THURSDAY, MARCH 19, 1981
AM
PHARMACOLOGY: NEWER INOTROPIC AGENTS
10:30-12:00

INTRAVENOUS AND ORAL AMRINONE THERAPY IN REFRACTORY HEART FAILURE: HEMODYNAMICS, EXERCISE RESULTS, AND SIDE EFFECTS
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Fourteen patients, age 40-76, 11 males, with cardiomyopathy (9 dilated, 5 ischemic) and refractory heart failure symptoms at rest and/or minimal exertion were treated with Amrinone by intravenous bolus (IVB), intravenous infusion (IVI) at 10 µg/kg/min, and orally at 1.6-4.0 mg/kg q8h. Hemodynamic monitoring was done before (pre) and for the first 3-8 days of therapy (Rx). The mean values ± standard error of the mean for cardiac index (CI, l/min/m^2), mean pulmonary artery wedge pressure (PWP, mm Hg), stroke volume index (SVI, ml/m^2), systemic resistance (R_S, units m^2), heart rate (HR), and mean arterial pressure (MAP, mm Hg) are listed below.

	CI	PWP	SVI	R_S	HR	MAP
Pre-Rx	1.8±.09	28±2.6	19±1.5	47±2.6	99±5.2	81±4.2
IVB-Rx	3.0±.13	21±2.3	32±2.5	27±1.9	95±4.1	76±4.7
IVI-Rx	3.0±.20	20±2.1	32±2.8	26±1.8	97±4.4	76±3.4
Oral-Rx	2.9±.23	19±2.3	30±2.7	28±1.9	100±3.9	79±3.3

In all 14 patients all 3 CI measurements on Rx were higher than pre-Rx ($P<.001$). In all patients this reproducibility held for PWP and R_S decreases and SVI increases ($P<.001$). For HR and MAP no reproducible pattern or significant change occurred ($P>0.1$). Naughton protocol treadmill exercise capacity (increasing 1 MET every 2 min) increased an average of 285 sec after 8-44 days on Amrinone in 4 of 6 patients able to walk. Platelet counts decreased in all patients by 88,000/mm^3 (avg) after 1 week of Rx, decreased to <100,000/mm^3 in 7 patients (associated with prolonged IVI Rx or oral Rx ≥3.0 mg/kg q8h in 6 of 7 patients) with no associated signs or symptoms, and improved in 2-4 days by decreasing the Amrinone dose. In conclusion, Amrinone is a promising potent inotrope, exhibits no hemodynamic tolerance up to 8 days of Rx, and can be used in doses not associated with thrombocytopenia.

HEMODYNAMIC AND METABOLIC EFFECTS OF TERBUTALINE IN PATIENTS WITH SEVERE HEART FAILURE
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To assess the hemodynamic and metabolic effects of terbutaline, a B_2 selective agonist, we evaluated 6 patients with severe heart failure secondary to ischemic heart disease by right and left cardiac and coronary sinus catheterizations. All other drugs were withheld prior to the study. Terbutaline was administered intravenously by constant infusion at 0.3 ug/kg/min for 30 minutes followed by 0.15 ug/kg/min for 60 minutes. The mean values ±S.D. are shown for heart rate (HR, beats/min), mean arterial pressure (MAP, mmHg), cardiac index (CI, L/min/m^2), stroke index (SI, ml/beat/m^2), pulmonary artery wedge pressure (PAW, mmHg), systemic vascular resistance (SVR, dynes sec cm^5/m^2), myocardial lactate extraction (EX_L,%) and myocardial oxygen extraction (EX_{O2},%). *P<0.05, #P<0.001.

	Control	30 min	60 min	90 min
HR	85±15	98±17*	96±16	96±20
MAP	87±17	87±20	82±20	88±22
CI	1.9±0.8	3.1±1.2*	3.0±1.2*	2.9±1.6*
SI	21.8±6.5	30.7±8.1*	30.7±8.4*	28.8±10
PAW	28.0±7.7	16.0±6.8*	15.8±5.1*	15.7±6.2*
SVR	1487±471	946±377#	938±440#	1125±529#
EX_L	19±41	24±26	28±24	26±29
EX_{O2}	61±8	63±12	64±10	62±11

The results of the study indicate that intravenous terbutaline produces beneficial hemodynamic effects without deterioration of myocardial metabolism as indicated by EX_L and EX_{O2}. The drug may prove to be a useful agent for patients with heart failure due to coronary artery disease.

ACUTE EFFECTS OF AMRINONE (5-AMINO-3,4'-BIPYRIDIN-6(1H)-ONE) ON SYSTEMIC BLOOD FLOW DISTRIBUTION.
Stanley Einzig, MD and Mary Ella Pierpont, MD; University of Minnesota; Minneapolis, Minnesota.

Amrinone (AM), a new cardiotonic agent, is used to treat refractory heart failure. However, the effect of this drug on blood flow (BF) in different vascular beds is unknown. We investigated the effect of AM on CO and on myocardial, cerebral, renal, intestinal, hepatic (arterial), pancreatic and skeletal muscle BF ("15" micron radionuclide labeled spheres) in 15 anesthetized dogs. Measurements were made during control (C) conditions, and 5 and 60 min. following intravenous AM injection. At 5 min. following AM at 1 mg/kg (n=7): mean Ao pressure was reduced by 8 mmHg from 118±7 (SE) mmHg ($P<0.01$); CO was unchanged from the C value of 125±8 ml/kg/min; LV and renal cortical BF were increased by 30% and 16% from C values of 1.07±0.05 and 6.12±0.24 ml/g/min, respectively ($P<0.05$ and $P<0.01$); and cerebral, intestinal, hepatic, pancreatic and skeletal muscle BF were unchanged from C values of 0.35±0.03, 0.56±0.14, 0.14±0.04, 0.29±0.04 and 0.04±0.01 ml/g/min, respectively, ($P>0.05$). The transmural distribution of LVBF (ie, Endo/Epi ratio) was reduced (1.08±0.03 vs 0.91±0.03, $P<0.002$). Similar changes in BF were present in dogs receiving 2 mg/kg (n=8), despite a greater reduction in mean Ao pressure (ie, 27 mmHg). At 60 min. post AM, LV and renal BF had returned to C values in both groups of dogs and the LV Endo/Epi ratio returned to 1.0. These studies suggest that with the exception of transient alterations in myocardial and renal perfusion, AM has minimal effects on systemic BF distribution under our experimental conditions.

THE EFFECT OF TERBUTALINE ON RIGHT AND LEFT VENTRICULAR FUNCTION AND SIZE IN OBSTRUCTIVE LUNG DISEASE.
Wayne Hooper, M.D., Robert Slutsky, M.D., Dale Kocienski, M.D., Kathy Witzum, M.D., Roger Spragg, M.D., William Ashburn, M.D., and Kenneth Moser, M.D., University of California, San Diego, Ca.

Terbutaline (T) is relatively B2 specific. T has been shown in CAD and COPD to increase LVEF and C.O. Its effects on RV function are not known. Eleven patients with severe COPD ($\overline{FEV_1}$=46%, MMEF .28) were studied by equilibrium radionuclide angiography before and serially after .25mgm T s/q. Six patients had depressed RVEF (<.45) before T.

	Control	25-30	50-60	115-120*
LVEF	.63±.03	.76±.03†	.72±.03†	.65±.03
LVEDV	106± 9	84± 9 †	94± 9	104± 9
LVSV	64± 5	61± 5	63± 5	66± 5
RVEF	.39±.03	.54±.03†	.52±.03†	.45±.03
RVDVU	3.58±.15	2.91±.15	2.88±.15	2.97±.15

(Statistics are mean ± SEM; *minutes after T; †p<.05 vs control; LVEDV=LV end diastolic volume; LVSV=LV stroke volume; RVDVU=RV diastolic volume units).

Serial values of expiratory flow rates after T did not change. There was no change in LVSV and an insignificant increase in cardiac output (↑10%) despite an increase in heart rate (↑14%, p<.01). Mean and diastolic blood pressures decreased (p<.05). While the RVDVU did not appear above to have significantly decreased, when examined at the time of peak increase in RVEF, the RVDVU had diminished (p<0.01) compared to before T. Therefore, T increases LVEF and RVEF while decreasing LV and RV size. We conclude that T may be potentially beneficial in COPD patients for its hemodynamic effects (inotropy, afterload reduction) despite its adverse chronotropic effect and lack of flow rate improvement in certain patients.

COMPARATIVE CARDIOCIRCULATORY ACTIONS OF NEW SELECTIVE BETA-1 AGONIST PRENALTEROL VS DOBUTAMINE: DEMONSTRATION OF EQUIVALENT BENEFICIAL EFFECTS ON CARDIAC PUMP PERFORMANCE IN CONGESTIVE HEART FAILURE

Kathleen Needham, BS; Najam A. Awan, MD, FACC; Mark K. Evenson, BS; Zakauddin Vera, MD, FACC; Dean T. Mason, MD, FACC, University of California, Davis.

To evaluate the efficacy of the new positive inotrope selective beta-1 receptor agonist prenalterol (PN) in therapy of severe chronic congestive heart failure (CHF) we compared the hemodynamic effects of intravenous PN (4mg) with dobutamine (DB; 10μg/kg/min) in 7 severe CHF patients. Measurements included: HR=heart rate, bpm; MBP=mean blood pressure, mmHg; LVFP=left ventricular filling pressure, mmHg; CI=cardiac index, L/min/M^2; SI=stroke index, ml/beat/M^2; SWI=stroke work index gm·m/M^2; TSVR=total systemic ventricular resistance, dsc^{-5}. Drug vs Control (C): * = p<0.01, + = p<0.001.

	HR	MBP	LVFP	CI	SI	SWI	TSVR
C	84	83	20	1.97	24	21	1702
PN	86	79	19	2.62*	30+	26*	1260+
C	87	84	20	1.99	24	22	1861
DB	92	79	18	2.76*	30*	27*	1223*

Therefore PN and DB equally raised LV pump function: prenalterol increased CI 24% while dobutamine elevated CI 27%,($p>0.05$). Moreover blood pressure, left ventricular filling pressure and heart rate were unchanged with both agents. These positive inotropic actions of PN were not accompanied by increased ventricular ectopy. Thus the beta-1 agonist prenalterol safely produces dobutamine-like salutary augmentation in cardiac function in patients with severe congestive heart failure. Importantly the availability of an oral formulation of prenalterol provides potential beneficial ambulatory therapy in patients demonstrating salutary acute responses. Thereby the new positive inotrope prenalterol is useful for therapy of severe congestive heart failure.

ACUTE AND FOLLOW-UP STUDIES WITH PIRBUTEROL IN HEART FAILURE

J.R. Dawson, MRCP; S. Reuben, PhD; P.A. Poole-Wilson, MD G.C. Sutton, MD, FACC, Hillingdon Hospital and Cardiothoracic Institute, London, U.K.

Pirbuterol, a beta-agonist with vasodilator and positive inotropic properties, has been investigated in 59 patients with chronic heart failure (NYHA Class III/IV). Hemodynamic measurements were made by Swan-Ganz catheter and cardiac output by thermodilution. The results represent values for control and peak response using various doses of pirbuterol(10-40mg). CI increased from 2.1±0.1 l/min/m^2 to 3.0±0.1 l/min/m^2 ($p<0.001$), left ventricular filling pressure (LVFP) and systemic vascular resistance(SVR) both fell from 25±1.5mm/Hg. to 19±1.5 mmHg. ($p<0.001$) and from 1830±70 dynes/sec/cm^5 to 1330±60/dynes/sec/cm^5 ($p<0.001$) respectively. Heart rate and blood pressure did not change. Subsequently patients began long-term treatment with pirbuterol 20mgs t.i.d. During preliminary follow-up (mean 4 months), 16 patients (27%) died; 11 of intractable heart failure, 3 suddenly, 1 from pulmonary embolism and 1 from a non-cardiac cause. 15 patients were withdrawn, 10 for lack of efficacy, the others because of side effects. 16 patients had repeat studies at 3 months. CI was 2.8±0.2, LVFP 17±4 and SVR 1350±150 all significantly improved from their initial control values ($p<0.001$). These indices were unchanged following a further challenge with pirbuterol(20mgs) suggesting that a maximal response had already been attained. Acute administration of pirbuterol improves pump performance, an effect which is sustained in some patients on long-term treatment. The high incidence of death and withdrawal in follow-up probably reflects the severity of disease in the population studied.

THURSDAY, MARCH 19, 1981
AM
RECANALIZATION OF OCCLUDED VESSEL DURING ACUTE PHASE OF MYOCARDIAL INFARCTION
10:30-12:00

TRANSLUMINAL RECANALIZATION DURING EVOLVING MYOCARDIAL INFARCT IN MAN.

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Coronary recanalization was attempted in 7 patients (pts) 3-5 hrs after clinical onset of myocardial infarct (MI). Group A: 2 pts with 100% and 2 pts with 99% obstruction (Obs) of the proximal RCA, unresponsive to nitroglycerin, underwent successful thrombus perforation, resulting in some antegrade flow. Intracoronary streptokinase (Stk) infusion (2000-4000 U/min) for 60 min improved Obs to 95, 90 and 40% with complete filling of the distal vessel. Reperfusion was associated with decrease in ST elevations, improvement of segmental wall motion, early appearance and peak of creatine kinase-MB and ventricular irritability. Follow-up: Segmental wall motion was improved to mild hypokinesis in 2 pts, to normal in 2 pts. Group B: Thrombus perforation was unsuccessful in 1 pt with 100% mid LAD Obs and in 2 pts with 99% mid LAD or 99% proximal CCA Obs. Thrombus perforation was unsuccessful because of inability to selectively catheterize the diseased vessel. Stk infusion did not change Obs; infarct related left ventricular segments remained akinetic. Lack of reperfusion might be related to non-selective infusion of Stk into the main LCA. Infusate was probably redistributed mainly in the normal left coronary system. Follow-up: Progression of 99% Obs to complete Obs in 2 pts. Prior akinetic segments remained severely hypokinetic. Conclusions: (1) Early reperfusion can salvage myocardial function. (2) Lysis of thrombus is more effective if preceded by perforation. (3) Stk infusion selectively into the obstructed artery appears necessary. (4) Reperfusion is associated with ventricular irritability and enzyme washout.

THE "REFLOW" AND "NO-REFLOW" MYOCARDIAL INFARCTION.

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It is known that after acute myocardial infarction (MI) a variable amount of reflow to the ischemic area may occur; and, that contraction band (CB) necrosis is a histologic marker for reflow. To determine how reflow affects clinical and pathologic features of the acute infarct, we studied 31 autopsied patients with acute MI and histologic evidence of sizeable reflow (defined as > 30% of total infarct being CB necrosis) and compared them to 39 with little or no-reflow (< 30% of infarct, CB necrosis). Comparing these 2 groups, there was no significant difference in age, sex, initial Killip class, blood pressure, primary ventricular arrhythmias, or heart block; and at autopsy no difference in heart weight, location or number of MI's, or extent of coronary artery disease. Patients with reflow MI's had less Q wave infarcts (12/31 vs 29/39, $p < .005$), more hypotensive episodes prior to the MI (13/31 vs 5/39, $p < .01$), smaller infarcts (16% LV vs 23% LV, $p < .05$), and shock or congestive heart failure as a less frequent cause of death than no-reflow MI's (9/31 vs 24/39, $p < .005$). Thrombi were found more frequently in the no-reflow patients (31/39 vs 8/31, $p < .005$). Of the patients with reflow infarcts, 28/31 had a patent coronary that fed the infarcted myocardium as opposed to only 9/39 patients with no-reflow MI's ($p < .005$).

The morphologic distinction of these 2 types of infarcts is compatible with the clinical concept of the occlusive thrombotic (no-reflow), and the spasm or hypoperfusion MI (reflow). Moreover, the morphologic data suggests that reflow may be associated with more arrhythmias, but greater myocardial salvage.

DISSOLUTION OF CORONARY ARTERY BYPASS GRAFT THROMBI BY STREPTOKINASE INFUSION

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Early post-operative(post-op)coronary artery bypass graft thrombosis may result in unstable angina requiring urgent reoperation. We report initial experience with thrombus dissolution by direct graft infusion of strepokinase at 26 hrs(pt 1)and 1½ hrs(pt 2)following onset of symptoms. Arteriography seven days post-op in pt 1(72 yo male) revealed total occlusion of the proximal right coronary artery(RCA) and RCA graft. Following guide wire penetration of the thrombus-filled graft, streptokinase, 10,000 units bolus and 1200 units/min, was infused for 90 min through a pre-formed brachial coronary catheter. Serial arteriography documented progressive thrombolysis, increasing distal graft visualization, and return of flow within the RCA. Death occurred 36 hrs later. Post-mortem examination showed extensive recent inferior and old anterior infarctions but patent RCA graft. Ten days post-op, arteriography in pt 2(66 yo female)revealed total occlusion of the proximal left anterior descending artery(LAD)and subtotal thrombotic occlusion of the LAD graft. Streptokinase was infused for 90 min through a 3.5 F transfemoral catheter positioned within the graft body. Gradual but partial thrombolysis resulted with relief of ischemic pain at 30 min and resolution of ST segment depression. Continued treatment with anti-platelet agents & anticoagulants resulted in near complete disappearance of thrombus and marked improvement in anterior wall contractility at arteriography 10 days later. We conclude that dissolution of acute graft thrombi by direct infusion of streptokinase is technically feasible. Additional studies will be required to define the clinical role of this technique.

SALVAGE OF JEOPARDIZED MYOCARDIUM BY NON-SURGICAL REPERFUSION (NSR) IN MAN

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Biplane LV cineventriculography was performed sequentially in 18 infarct pts., in whom reperfusion was achieved within 8 ± 7 hrs after onset of chest pain by intracoronary infusion of streptokinase (SK) (2000 U/min) (A). EF was 51.4 ± 9.8 % prior to reperfusion and 54.8 ± 8.9 % after completion of SK-infusion ($p < 0.025$); length of the AKS decreased from 10.2 ± 6.1 cm to 7.1 ± 4.9 cm ($p < 0.025$). LVEDP decreased from 21 ± 9 to 18 ± 7 mmHg ($p < 0.025$). Inspection during bypass surgery in 10 pts. 40 ± 23 days after reperfusion and microscopic examination of transmural myocardial biopsies in 3 pts. revealed the bulk of reperfused myocardium to be viable. Hemodynamic data prior to reperfusion and in the chronic stage of MI (prior to aortocoronary bypass surgery) were compared with data of a retrospectively matched group of conventionally treated pts. (B) who had acute angiography at a time when NSR was not yet available. Control angiography in the chronic stage showed: persistent occlusion of infarct vessel(B_1, n=9), spontaneous recanalization of initially obstructed infarct vessel (B_2, n=9).

		A	B_1	B_2
EF (%)	acute	49.9 ± 12	52 ± 6.6	51 ± 8.1
	chronic	57.4 ± 12.7	43.4 ± 7.6	52 ± 12.2
AKS (cm)	acute	9.2 ± 6.2	7.7 ± 4.0	9.1 ± 4.9
	chronic	4.5 ± 6	9.8 ± 5.5	7.1 ± 6.9

×=p<0.025

Aneurysm formation occurred in 3 Co- and 2 Cr-pts., but not in Group A. Preservation of R-waves was more extensive in Group A. The data demonstrate improvement of LV function early after NSR and suggest that jeopardized myocardium was salvaged.

LYSIS OF CORONARY ARTERY THROMBOSIS WITH INTRACORONARY STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION

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Intracoronary (IC) infusion of streptokinase (SK) at 2000 Iu/minute was performed in 11 patients (pts) with acute transmural myocardial infarction (AMI) at (mean±SD) 10±4 hours following onset of chest pain (range 4-15 hours). Lysis of coronary artery thrombus by IC SK relieved the total occlusion responsible for AMI in 8 pts by 30 minutes of SK infusion. Three pts had high grade (>50% reduction in luminal diameter) stenosis without total obstruction. Angiographic left ventricular (LV) ejection fraction (EF), LV end-diastolic pressure (EDP), LV stroke volume (SV) and LV stroke work index (SWI) pre and post IC SK were as follows:

	PRE		POST	p
EF(%)	42±13	(range 28 to 67)	48±12	ns
EDP(mmHg)	26±8	(range 17 to 41)	32±11	ns
SV(cc/beat)	55±34	(range 24 to 113)	53±18	ns
SWI(gm-m/M^2)	48±23	(range 25 to 87)	41±8	ns

Moreover, LVEF determined with gated cardiac blood pool imaging did not change from immediately post IC SK to hospital discharge (52±16% vs 52±15%, p=ns). Two pts demonstrated improvement in segmental wall motion abnormalities following lysis of coronary thrombus with increase in LVEF of 24% and 13%. LVEF increased by 12% in two additional pts without change in segmental wall motion abnormalities. These data suggest 1) IC SK resulted in lysis of coronary artery thrombus in pts with AMI 2) Indices of global LV performance do not significantly (p=ns) change in most pts with AMI either immediately post IC SK or at hospital discharge when studied at a mean of 10 hours post chest pain.

INTRACORONARY STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION: ASSESSMENT BY Tl-201 SZINTIGRAPHY

Gerhard Schuler,Klaus v. Olshausen, Helmut Mehmel, Jochen Senges, Jochen Manthey, Wolfgang Mäurer, Wolfgang Kübler,FACC; Med. Uni-Klinik,Heidelberg,Germany

Intracoronary infusion of streptokinase (S) has been advocated as a means to salvage jeopardized myocardium in acute coronary occlusion. We used seven-pinhole Tl-201 tomography to study the effect of this intervention in 10 patients (pt) with electrocardiographic evidence of acute myocardial infarction and less than 4 hours of chest pain. There was no history of previous infarction in any pt. Coronary cineangiography (CA), performed prior to S, showed occlusion of one major coronary artery branch associated with a dyskinetic area. Restitution of flow was achieved in 9 pts; in 1 pt S failed to reestablish flow. Szintigrams were obtained before (CONTROL) and following S at 24 hours and 4 weeks. At CONTROL a large perfusion defect was present in all pts; at 24 hours two groups of pts could be identified: in 7 pts there was only marginal reduction of infarct size as compared to CONTROL although reflow was achieved as early as 2.5 hours after onset of symptoms. In these pts CA failed to demonstrate collateral coronary circulation supplying the infarcted area. However, in two pts with extensive collaterals there was marked improvement of Tl-201 uptake. Both groups did not differ significantly in time from onset of symptoms to reestablishment of flow. No change was noted in one pt in whom the vessel remained occluded. At 4 weeks only insignificant additional improvement of Tl-201 uptake was noted. We conclude: Lysis of acute coronary thrombosis is readily accomplished by S in most pts; however significant reduction of infarct size as assessed by Tl-201 szintigraphy seems to be largely dependent on the presence of collateral circulation.

THURSDAY, MARCH 19, 1981
AM
SURGERY FOR CORONARY ARTERY DISEASE—2
10:30-12:00

FACTORS AFFECTING MORTALITY AFTER MITRAL VALVE REPLACEMENT COMBINED WITH CORONARY BYPASS GRAFTING

Bernard Gersh, MD, FACC; Francisco J. Puga, MD; Ronald E. Vlietstra, MD, FACC; Lila R. Elveback, PhD; Steven L. Yeager, MD; William D. Edwards, MD; Gordon K. Danielson, MD, FACC; James R. Pluth, MD, FACC, Mayo Clinic, Rochester, MN.

At the Mayo Clinic from 1972-1978, the 30-day mortality for isolated mitral valve replacement (MVR) was 5.3% (41 of 779), whereas that for MVR plus coronary bypass graft surgery (CABG), 1970-1978, was 13.3% (10 of 75). The aim of this study was to identify by multivariate methods the factors resulting in the high early mortality in the MVR plus CABG group. Clinical, laboratory, and surgical variables were included. There was a major difference between the sexes: the females were older, had more severe coronary artery disease (CAD), had a smaller proportion of diseased vessels grafted, and had a higher early mortality (8 of 22 or 36% versus 2 of 53 or 4% for males). Nine of the 10 early deaths could be identified by means of 3 factors: the Gensini measure of the severity of CAD, the adequacy of left coronary revascularization, and the presence of LV aneurysm. This combination of variables correctly classified 91% of the patients. For rheumatic or ischemic etiology (n=47), the early mortality was 20%, whereas CAD was less severe and there were no deaths in patients with primarily degenerative mitral valve disease (n=20). For the 65 30-day survivors, the subsequent 3-year survival was 71% (51% in females, 76% in males). The cardiothoracic ratio was the only variable that discriminated between late deaths and the 3-year survivors. We conclude that the early mortality of MVR plus CABG is markedly influenced by the extent of CAD and the adequacy of revascularization. Late mortality, however, is predominantly affected by ventricular function.

CORONARY ANGIOGRAPHY AND CORONARY ARTERY BYPASS SURGERY IN ELDERLY PATIENTS

Bernard Gersh, MD, FACC; Robert L. Frye, MD, FACC; Richard A. Kronmal, PhD; Elizabeth Cardis, BS; Thomas J. Ryan, MD, FACC; Arthur J. Gosselin, MD, FACC; George Kaiser, MD, FACC; Thomas Killip III, MD, FACC, and all participants in the Coronary Artery Surgery Study (CASS).

This study describes 2,035 patients (pts) ≥65 years old with coronary artery disease entered in the CASS registry and the complications of coronary angiography and bypass surgery (CABG) in this group. Ages ranged from 65-82 years; 73% were males. The predominant symptom was angina pectoris in 86% and cardiac failure in 6%. In 51%, angina pectoris was unstable. Angiography documented triple-vessel disease in 53%, double-vessel in 26%, and single-vessel in 17%. Disease of the left main coronary artery (≥50% stenosis) was present in 15%. Ejection fraction was <50% in 32% of pts. Complications of angiography included death in 0.25%, nonfatal myocardial infarction in 0.6%, and neurologic complications in 0.5%. CABG alone was performed in 997 pts (49%), with a hospital mortality of 5%. Pts were divided into three age groups: 1, 65-69 years; 2, 70-74 years; and 3, ≥75 years. Results were as follows:

No. of pts	Group	Hospital surgical mortality
735	1	4.5%
221	2	6.3%
41	3	9.8%

We conclude that in patients ≥65 years of age, the mortality of coronary angiography is low whereas that of CABG is increased in comparison with a 1.8% hospital mortality in 6,438 CASS pts <65 years old.

HYPERLIPOPROTEINEMIA (HLP) AS A SIGNIFICANT RISK FACTOR FOR PULMONARY EMBOLISM (PE) IN CORONARY ARTERY BYPASS (CABG) PATIENTS

Eric C. Hanson, MD and Frederick H. Levine, MD
Massachusetts General Hospital, Boston, MA 02114

Although PE is a rare complication following cardiac surgery, a notable association of PE in hyperlipoproteinemic patients following CABG procedures prompted us to define the incidence of PE in this group. A retrospective study of all patients suffering PE following cardiac surgery from 1975 through 1979 was undertaken and lipoprotein profiles of these patients were evaluated. Of over 4,800 patient records, 26 patients (19 male, 7 female) were identified who presented with the definite clinical, laboratory, and radiologic evidence of PE in the post-operative period. Twenty had undergone coronary artery bypass grafting, and the remaining six had undergone other cardiac procedures. Of the 20 CABG patients, 19 (95%) were found to have HLP (14 Type II patients, 70%; 5 Type IV patients, 25%). Only one of the six other patients had HLP, a patient who had an aortic arch aneurysm resection who was Type II. There were four hospital deaths (4/26, 15%), all related to PE and all were Type II patients who had undergone CABG procedures. Since patients with HLP comprise less than 10% of our CABG population the incidence of PE in this group is highly significant ($p<.001$). Experimental evidence has shown that patients with HLP, especially Type II, have increased platelet adhesiveness and clotting abnormalities consistent with a hypercoagulable state. This retrospective study clinically confirms that finding and suggests that early postoperative anticoagulation therapy in patients with HLP, particularly Type II, may be indicated to reduce thromboembolic complications.

IMPROVED GRAFT PATENCY WITH ANTIPLATELET DRUGS IN PATIENTS TREATED FOR ONE YEAR FOLLOWING CORONARY BYPASS SURGERY.

B Greg Brown, MD,PhD, Ramon A Cukingnan, MD, Lacy Goede, BS, Maylene Wong, MD, Henry Fee, MD, Jack Roth, MD, John Wittig, MD, Joseph Carey, MD, Wadsworth VA Hosp, UCLA, L.A., CA.

Does antiplatelet therapy (APT) improve saphenous vein graft patency? 147 consecutive patients (pts) were enrolled in a randomized, doubly blinded, risk-stratified, prospective trial comparing aspirin 325 mg tid plus dipyridamole 75 mg tid (A/D), or aspirin (A), with double placebo (P). 123 patients completed surgery, drug initiation 67±27 (SD) hours post-op, 5 clinic visits, and recath at one year. Overall predictors of graft patency were coronary lumen diameter at the point of anastomosis (D_{an}), the % proximal stenosis in the grafted artery (%S), graft flow (Q_g), and the % reactive hyperemia (%RH) after a 15 second graft occlusion. Results, in terms of assigned therapy (AR_x): APT did not benefit grafts to arteries with $D_{an} \leq 1.5$mm, or grafts with $Q_g \leq 40$ml/min or with %RH ≥ 15% above baseline flow. But a substantial trend in favor of APT (A or A/D) was seen in the overall group. Strong favorable trends or statistically significant benefits were seen in certain large subsets. All grafts were patent in 57% of 44 pts on P, 73% of 37 pts on A, and 63% of 42 pts on A/D.

	GRAFT OCCLUSION FREQUENCY (NO. OF GRAFTS AT RISK IN GROUP)			
AR_x	All Grafts	D_{an}>1.5mm	Q_g>40ml/min	%RH<15%
P	21.1%(147)	18.8%(112)	22.8% (101)	33.8% (71)
A	12.2%(115)	8.2%* (85)	9.5%+ (84)	17.2%* (58)
A/D	16.3%(135)	10.4% (96)	8.3%‡ (84)	20.0% (65)
APT	14.4%(250)	9.4%+ (181)	8.9%‡ (168)	18.7%+ (123)

χ^2 comparison of drug with P: *=p<.05, +=p<.02, ‡=p<.01

The most common and generally most important subsets of diseased arteries are those with D_{an}>1.5mm or which require Q_g>40ml/min. Antiplatelet therapy reduces by 50-61% the early occlusion of grafts to those arteries. Thus post-op APT is recommended, unless contraindicated, for most bypass patients.

THE CLINICAL USEFULNESS AND FEASIBILITY OF DETERMINING CORONARY ARTERY BYPASS GRAFT PATENCY BY CONTRAST ENHANCED COMPUTED TOMOGRAPHY DURING THE EARLY POSTOPERATIVE PERIOD

Charles R. McKay, MD; Bruce H. Brundage, MD, FACC; Robert J. Herfkens, MD; Martin J. Lipton, MB, ChB, FACC; Kevin Turley, MD, FACC; Daniel J. Ullyot, MD, FACC; Paul A. Ebert, MD, FACC, University of California, San Francisco, Ca.

Eight male patients (PTS) with severe coronary artery disease received 20 saphenous vein coronary artery bypass grafts (CABG). Soon after surgery (6 of 8 PTS within 4 days of surgery), graft patency was evaluated by contrast enhanced computed tomography (CT) using a peripheral vein for injection of contrast medium. In 4 of the 8 PTS the following clinical situations raised the question of early graft occlusion: recurrent ventricular fibrillation with myocardial infarction, recurrent pericardial tamponade, low intraoperative graft flow measurements and a friable aorta which required 1 complex "Y" graft with 2 vein-to-vein anastomoses to bypass 3 vessels. All studies were completed within 1 hour and were well tolerated by the PTS without significant morbidity. CT scans demonstrated that all 20 grafts were patent, and eliminated early graft occlusion as a clinical problem in these PTS. The study shows that CT imaging of CABG in the early postoperative period is easy to perform, has no significant morbidity, and yields clinically useful information. Recognition of graft occlusion within 48 hours of surgery should be possible with this technique. Assessment of CABG in the early postoperative period by CT may be a useful reference for repeat CT studies in the long term follow-up of these PTS.

THURSDAY, MARCH 19, 1981
AM
ARTERIAL ARRHYTHMIAS
10:30-12:00

ATRIAL TACHYCARDIA. THE PAROXYSMAL VERSUS THE PERMANENT FORM.

Hein J.J. Wellens, MD, FACC; Pedro Brugada, MD; David Ross, MD; Frits W.H.M. Bär, MD; Eddy J.D.M. Vanagt, MD; Willem R.M. Dassen, PhD, Dept. of Cardiology, University of Limburg, Annadal Hospital, Maastricht, The Netherlands

In 12 consecutive patients(P) with atrial(A) tachycardia (T) A mapping, initiation(I) and termination(Te) of T by programmed stimulation(PS) and the effect of carotid sinus massage(CSM), Atropine (9P) and Verapamil (10P) were studied. In 7P T originated in the A septum, in 4P in the right and in 1P in the left atrium. In 7P T was paroxysmal (group 1), in 5P T was permanent (group 2). P of group 1 were older than group 2 ($p<0.001$). There were no differences in sex or heart rate during T. In all P of group 1 and none of 2 I and Te of T was possible by PS, in all P of group 2 T could be reset during PS. CSM terminated T in all P of group 1 and one of group 2. Atropine (1mg i.v.) accelerated T in 4/6 P of group 1 and 3/3 of group 2. Verapamil (10mg i.v.) slowed or terminated T in 5/6 P of group 1 and had no effect (2/4P) or accelerated T (2/4P) in group 2. Exercise accelerated AT in 4/4 P of group 2. Conclusion: 1) AT of the paroxysmal form fulfills criteria for a re-entry or triggered automaticity mechanism and can be suppressed by vagal manoeuvres and drugs. Follow-up study showed complete suppression of paroxysmal AT by drugs. 2) AT of the permanent form seems to be based on abnormal automaticity. The area of impulse formation can be invaded and reset but T cannot be terminated by PS, vagal manoeuvres or drugs. Follow-up study showed failure to suppress T by any of the existing drugs.

INOTROPIC CONTRACTILE RESERVE: A USEFUL PREDICTOR OF INCREASED FIVE YEAR POSTOPERATIVE SURVIVAL AND IMPROVED LEFT VENTRICULAR FUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE AND A DEPRESSED EJECTION FRACTION

Richard Nesto, MD; Lawrence H. Cohn, MD, FACC; John J. Collins, Jr., MD, FACC; Joshua Wynne, MD, FACC; B. Leonard Holman, MD, FACC; Peter F. Cohn, MD, FACC, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

The increase in ejection fraction (EF) produced by post-extrasystolic potentiation or epinephrine infusion (PESP/EPI) has been used to demonstrate inotropic contractile reserve (ICR) in patients with coronary artery disease and a depressed EF (<.50). Prior studies have shown that $\Delta EF \geq .10$ after PESP/EPI is helpful in discriminating those patients with better short term (1 yr) prognosis whether treated medically or surgically. Because no data are available concerning long term follow-up, the present study related ICR to 5 yr postoperative prognosis in 35 patients receiving PESP/EPI between 1971-74. LV function was assessed with radionuclide ventriculograms whenever possible. Results are as follows:

	$\Delta EF \geq .10$		$\Delta EF < .10$
No. of patients	20		15
Early deaths (<2 mo)	2		6
Late deaths (≥2 mo)	2		4
5 yr survival	16/20 (80%)	p<.01	5/15 (33%)
Radionuclide ventriculograms	6		3
Increase in EF from preoperative contrast LV gram (mean ± SEM)	.20 ± .05	p<.01	0 ± .08

Thus, ICR, as demonstrated by $\Delta EF \geq .10$ after PESP/EPI, is a useful predictor of increased 5 yr postoperative survival and improved LV function in patients with coronary artery disease and a depressed EF.

Disopyramide Phosphate in Wolff-Parkinson-White Syndrome.

Charles R. Kerr, M.D.; Eric N. Prystowsky, M.D., F.A.C.C.; Warren M. Smith, M.D.; John J. Gallagher, M.D., F.A.C.C. Duke University Medical Center, Durham, North Carolina.

We evaluated the electrophysiological effects of disopyramide phosphate(DP) in 12 patients with Wolff-Parkinson-White syndrome(WPW). Electrophysiological studies were done during a control period, following intravenous DP, and after 4 days on oral DP (1000-1200 mg/day). Reciprocating tachycardia and atrial fibrillation(AF) were induced in all patients. The cycle length and ventriculo-atrial interval during reciprocating tachycardia and the shortest and mean RR intervals during AF are shown in the following table (mean ± SD). P values are comparisons to control.

	Control	Intravenous DP	Oral DP
Cycle length (msec)	331±53	342±57	370±68*
V-A interval (msec)	118±44	127±45**	151±63**
AF-Shortest RR (msec)	169±18	226±24***	248±36***
AF-Mean RR (msec)	225±58	329±62**	360±93***

* $p < 0.025$, ** $p < 0.005$, *** $p < 0.001$

Following DP the episodes of AF were shorter and self-terminating. Despite prolonging the cycle length of reciprocating tachycardia, DP did not prevent its induction. Accessory pathway refractoriness prolonged following oral DP in all 6 patients in whom it could be assessed. No acute hemodynamic side effects were observed but 4 patients developed gastrointestinal or anticholinergic side effects on oral DP. Seven patients elected to have surgical interruption of their accessory pathways while 5 have been successfully treated with oral DP. Thus DP appears to have beneficial electrophysiological effects in patients with WPW. The ventricular response during AF is markedly slowed through prolonged refractoriness in the accessory pathway and the cycle length of reciprocating tachycardia is lengthened through slowed conduction in the pathway.

CHARACTERIZATION OF THE ONSET OF ECTOPIC ATRIAL TACHYCARDIA WITH A-V BLOCK.

Joaquin G. Arciniegas, MD; Vance J. Plumb; Albert L. Waldo, MD, FACC, University of Alabama in Birmingham, Birmingham, Alabama

Ectopic atrial tachycardia with A-V block (EAT) is a poorly understood rhythm. We analyzed the onset of 52 episodes of spontaneous EAT occurring in 9 patients free of digitalis toxicity. All patients were originally in sinus rhythm. During these episodes, bipolar atrial electrograms (AEG) were recorded simultaneously with at least one surface ECG lead. To establish the presence of EAT, the rhythm had to have a cycle length less than 273 msec (220 beats/min), an isoelectric segment between P waves and evidence of A-V block at some time during the tachycardia. Three distinct patterns of onset of EAT were appreciated. In 6 instances, EAT was preceded by transient atrial fibrillation of variable duration (12 to 20 seconds). In 4/6, gradual regularization of the AEG during atrial fibrillation occurred. In 2/6, EAT abruptly replaced atrial fibrillation. In 15 instances, EAT started de novo, the cycle length of the 1st beat being the same as the cycle length of the EAT. In 31 instances, EAT was started by a late premature atrial beat (coupling interval 74-88% of the preceding sinus cycle). This was followed by progressive shortening of the cycle length of the 2nd and 3rd beats of EAT, followed by regularization of the EAT at a longer cycle length than that of the 3rd beat. In this latter group, the principles of traditionally accepted mechanisms (automaticity and reentry) of arrhythmias are not followed. These data show a close interrelationship between EAT and atrial fibrillation and also suggest that more than one underlying mechanism of EAT may exist.

ATRIAL EXCITABILITY AND CONDUCTION IN PATIENTS PRONE TO ATRIAL FIBRILLATION

Ross J. Simpson, Jr., MD; James R. Foster, MD; Leonard S. Gettes, MD, University of North Carolina, Chapel Hill, N.C.

Atrial fibrillation occurs frequently in patients (pts) with prolonged P waves. To test the hypothesis that abnormalities of atrial excitability or conduction are found in these patients, we defined atrial strength interval curves, late diastolic threshold, and the conduction time of early and late premature beats in 7 pts with P waves of < 115 msec (Group I) and 13 pts with P waves ≥ 115 msec (Group II). The increase in conduction time of early compared to late premature beats was measured from the high right atrium to low septal right atrium (A_{HRA}-A_{HIS}) and coronary sinus (A_{HRA}-A_{LA}). Only Group II patients had abnormal sinus node function (3/13) or history of atrial fibrillation (6/13).

The conduction time of premature beats in late diastole was similar in both groups. In Group I pts the conduction time of early premature beats increased slightly. In Group II pts conduction time of early premature beats increased dramatically and the difference between the maximum increase in conduction time of Group I and Group II pts was significant (A_{HRA}-A_{HIS}: 5±10 vs 30±20, $p<.005$; A_{HRA}-A_{LA}: 5±15 vs 30±15, $p<.05$).

Late diastolic threshold was lower in Group I than in Group II pts (0.8±2 vs 1.3±2, $p<.005$). There was no difference between Group I and II in latency, refractory periods or presence of an early diastolic "supernormal" excitable period.

Conclusion: The marked conduction slowing of early atrial premature beats in patients with large P waves may explain their propensity to atrial fibrillation.

SINUS NODE FUNCTION AFTER CARDIAC TRANSPLANTATION

Alan F Mackintosh MRCP; David J Carmichael MRCP; Christopher Wren MRCP; Terence A English FRCS; Michael C Petch MD, Papworth Hospital, Cambridge, England

Cardiac transplantation produces a permanently denervated donor sinus node and provides an opportunity for studying the human sinus node separated from the autonomic nervous system. Twelve patients have received transplants at Papworth Hospital and temporary atrial epicardial wires were used in 6 to explore sinus node function during the first 3 weeks after operation. On most days recordings were made of the cycle length, the sinus node recovery time (SNRT), and the sinoatrial conduction time (SACT) calculated by pacing slightly faster than the spontaneous rate for 9 beats.

For the first 4 days the rhythm was unstable and all 6 patients demonstrated abnormal nodal function. After this period 2 patients showed a stable atrial rhythm with normal SNRT and SACT. Another patient temporarily developed a slow junctional rhythm soon after pacing associated with a prolonged SACT; both returned to normal after 9 days. These 3 patients are alive. The other 3 patients showed less stable rhythms. The SNRT was often markedly prolonged (maximum 12 seconds) and pronounced secondary slowing occurred after pacing. These 3 patients have died. One died while undergoing ambulatory monitoring; the tape showed progressive bradycardia leading to asystole after 16 minutes. One collapsed in circumstances suggestive of a fatal arrhythmia and the third died from uncontrolled rejection.

In our experience sinus node dysfunction can occur after transplantation and when present may be particularly dangerous as the normal escape mechanisms seem unreliable.

ENHANCED VAGAL TONE SHORTENS ATRIAL REFRACTORINESS AND FACILITATES INDUCTION OF REPETITIVE ATRIAL RESPONSES IN MAN.

Eric N. Prystowsky, MD, FACC; Gerald V. Naccarelli, MD; Warren M. Jackman, MD; Robert L. Rinkenberger, MD; James J. Heger, MD; Douglas P. Zipes, MD, FACC, Krannert Institute of Cardiology, Indiana University School of Medicine and V.A. Medical Center, Indianapolis, Indiana.

Although enhanced vagal tone (EVT) decreases atrial refractoriness in animals, published data on effects of ouabain and atropine suggest the opposite may occur in man. The purpose of this study was to determine the effect of EVT on right atrial effective (ERP) and functional (FRP) refractory period in man. Twelve patients (pts) had electrophysiology study using standard intracardiac techniques. A specially made collar connected to a vacuum source was placed around the pt's neck. EVT was produced during neck suction using intracollar negative pressures (INP) of -50 to -60 mmHg. INP, induced for 2 seconds during sinus rhythm, increased spontaneous sinus cycle length from 837 ± 96 to 1136 ± 273 msec (mean ± 1SD, $p<.001$). Atrial ERP and FRP were determined before and during application of INP. Atrial ERP and FRP significantly decreased during INP (241 ± 24 to 230 ± 20 msec, $p<.01$, and 272 ± 32 to 262 ± 29 msec, $p<.01$ respectively). During refractory period determinations, repetitive atrial responses were induced in 3 pts and occurred only during EVT. Systemic arterial blood pressure remained constant during INP. After atropine (0.03 mg/kg IV) no decrease in atrial refractoriness occurred during INP (2/2 pts). In conclusion: 1) EVT mediated via muscarinic receptors shortens atrial ERP and FRP in man, and 2) facilitates induction of repetitive atrial responses; 3) the neck collar provides a method to evaluate the effects of EVT on electrophysiologic properties in man.

THURSDAY, MARCH 19, 1981
AM
VENTRICULAR ARRHYTHMIAS II: LOCALIZATION OF FOCUS AND TREATMENT
10:30-12:00

ACTIVATION MAPPING IN SINUS RHYTHM IN PATIENTS WITH VENTRICULAR TACHYCARDIA-RELATIONSHIP TO CYCLE LENGTH AND SITE OF ORIGIN

Scott R. Spielman, MD; Leonard N. Horowitz, MD,FACC; Allan M. Greenspan, MD,FACC; William J. Untereker, MD, FACC; Michael B. Simson, MD,FACC; John A. Kastor, MD, FACC; Mark E. Josephson, MD,FACC. Hospital of the University of Pennsylvania, Philadelphia, Pa.

Eight patients with 10 morphologically distinct, clinically occurring ventricular tachycardias (VT) and coronary artery disease (CAD) underwent catheter (1 mm and 1 cm interelectrode distances) endocardial activation mapping in sinus rhythm (NSR) at 12-15 left ventricular sites. In all patients fragmented electrograms were recorded within the infarction zones that began within and outlasted the surface QRS by 15-95 msec (m=51.6±30.4). The cycle length of each VT (range 250-450 msec m=346±64.5) was directly related to the duration of activation in the longest local endocardial electrogram in NSR (range 100-170 msec m=137.5±26.1) with r=.807 ($p<.005$). The endocardial electrogram with the longest duration of fragmented activity was at the site of origin of 8/10 VTs. Epicardial mapping at 35-65 sites was also performed in NSR at the time of arrhythmia surgery in all 8 patients. Late epicardial potentials were only observed in 1 patient and were distant from the site of origin.

We conclude that fragmented electrograms recorded by catheter endocardial mapping identify areas of slow conduction that may participate in or be a final common pathway for the reentrant circuit in patients with VT-CAD.

SURGICAL THERAPY FOR RIGHT VENTRICULAR TACHYCARDIA

Jay W. Mason, MD, FACC; Edward B. Stinson, MD, FACC; David L. Ross, MD; Kaylyn Bockemuehl, RN, Stanford University Medical Center, Stanford, CA.

Four patients, 2 women ages 20 and 25 and 2 men 26 and 58 years, with recurrent right ventricular tachycardia (VT) which was resistant to therapy with 5 or more antiarrhythmic agents, including at least one experimental drug, underwent right ventriculotomy and/or myocardial resection at sites of early electrical activity determined by intraoperative activation sequence mapping during ventricular tachycardia. Three patients had right ventricular myocardial disease, characterized by fibrosis, hypertrophy and fatty infiltration, and one (25F) had no identifiable cardiac disease. All had normal left ventricles. The latter patient had a single VT morphology localized to the pulmonary outflow region, where a single 3cm ventriculotomy rendered VT uninducible. The other 3 patients (58M, 26F, 20F) had 3, 6, and 9 VT morphologies respectively, requiring multiple sequential ventriculotomies, full thickness resections or subendocardial resections of the right ventricle at successively identified early sites. None of the four patients had strikingly delayed epicardial electrical activity during NSR and even mildly late activity did not uniformly correspond to early sites during VT. Three of the four patients are free of arrhythmias and drugs 11, 9 and 2 months after surgery; one patient (20F) is now well controlled on encainide at 2 months. We conclude that drug resistant ventricular tachycardia in non-ischemic disease or even in a structurally normal heart can be treated successfully by surgery with mapping; that an as yet poorly understood myocardial disease may involve the right ventricle alone and cause VT; and that multiple VT morphologies are characteristic of this disease.

PROGRAMMED PREMATURE STIMULATION AS A GUIDE TO ANTI-ARRHYTHMIC THERAPY FOR MALIGNANT VENTRICULAR ARRHYTHMIA IN THE ABSENCE OF AMBIENT ECTOPY

Philip J. Podrid, MD, FACC; Arno Schoeneberger, MD; Bernard Lown, MD, FACC; Jeffery Matos, MD; James Porterfield, MD: Elizabeth Corrigan, MD, Cardiovascular Laboratories, Harvard School of Public Health, Boston, MA.

Among 180 patients (PTS) with recurring malignant ventricular arrhythmias (VA), 34 (19%) had little ectopic activity precluding antiarrhythmic (AA) drug testing. These PTS were subjected to programmed premature stimulation (PPS) to provoke multiple repetitive responses (MRVR) defined as 3 or more successive ventricular beats following the premature stimulus. Our aim was to determine if this endpoint rather than long runs or sustained ventricular tachycardia (VT) could be used to select an effective AA program. A right ventricular pacing wire was left in place for 1 to 2 weeks and was employed for PPS utilizing 1 to 3 extra stimuli at both 2x and 3x mid-diastolic threshold. Testing was performed during both ventricular pacing and sinus rhythm. In 30 PTS with MRVR, a total of 236 drug tests were conducted (7.6/pt). In 4 patients MRVR could not be produced. In 25 of the 30 patients MRVR was abolished by one or more AA agents and the AA drug suppressing MRVR was used for chronic maintenance therapy. After a mean followup of 15.6 months (1-29) one patient has had recurrence. Complications were infrequent, with sustained VT occurring in only 6.2% of tests; ventricular burst terminated 3.7% while 2.5% required cardioversion. Ventricular fibrillation was not precipitated. We conclude that PPS utilizing MRVR as an endpoint is as effective as but safer than provoking VT as a guide to AA therapy. It was effective in 25 or 34 PTS (74%) studied.

ELECTROPHYSIOLOGIC STUDIES BEFORE AND AFTER AORTOCORONARY BYPASS IN PATIENTS WITH OUT-OF-HOSPITAL VENTRICULAR FIBRILLATION

Hasan Garan, MD; Jeremy N. Ruskin, MD, FACC; John DiMarco, MD, Cardiac Unit, Massachusetts General Hospital, Boston, MA.

Electrophysiologic studies (EPS) with programmed ventricular stimulation (PVS) were performed in 7 patients undergoing aortocoronary saphenous vein grafting (ACSVG) following out-of-hospital ventricular fibrillation without acute myocardial infarction. Five patients had EPS before ACSVG. PVS induced ventricular fibrillation in 2 patients and nonsustained polymorphic ventricular tachycardia (5-20 beats) in 3 others off all antiarrhythmic drugs. All 7 patients underwent uneventful ACSVG without perioperative myocardial infarction. Two weeks after ACSVG all 7 patients underwent EPS with PVS. Three patients had nonsustained polymorphic ventricular tachycardia with PVS after ACSVG. Two patients had no inducible ventricular arrhythmia during EPS after ACSVG. The remaining two patients had PVS-induced ventricular flutter during EPS after ACSVG. In patients with electrically-induced ventricular arrhythmia after ACSVG, serial EPS with PVS were performed to define effective antiarrhythmic regimen, whereas patients with no electrically-inducible ventricular arrhythmia were discharged off antiarrhythmic drugs. All 7 remained free of arrhythmias with a follow-up period of 2 to 24 months. We conclude that in patients with high grade ventricular irritability the effect of ACSVG on electrical instability is not predictable and pre- and post-op EPS constitute an important port of their evaluation and treatment.

SLOW VENTRICULAR ACTIVATION DETECTED ON THE BODY SURFACE IN PATIENTS WITH VENTRICULAR TACHYCARDIA AFTER MYOCARDIAL INFARCTION

Michael Simson, MD, FACC, Scott Spielman, MD, Leonard Horowitz, MD, FACC, Mark Josephson, MD, FACC, Alden Harken, MD, FACC and John Kastor, MD, FACC, Hospital of the University of Pennsylvania, Philadelphia, PA.

Using advanced ECG processing, we have found a distinctive, low amplitude, high frequency signal in the late QRS which identified patients (pts) with ventricular tachycardia (VT) after myocardial infarction (MI). We studied the origin of that signal in 7 pts with inducible VT after MI using catheter endocardial and intra-operative epicardial mapping during sinus rhythm. All pts had ventricular aneurysms. Twelve left ventricular endocardial sites and 32-54 epicardial sites were studied. Bipolar XYZ ECG leads were signal averaged and processed with a bi-directional, 25 Hz high-pass digital filter.

Low amplitude, delayed, fractionated electrograms were recorded in all pts at 4.6 ± 2.6 sites/pt. All sites demonstrating fractionated electrograms were within the infarcted zone and 87% were endocardial. The fractionated electrograms lasted 89 ± 31 msec and ended 120 ± 36 msec after QRS onset. When analyzed for timing, the fractionated and delayed electrograms corresponded to the low amplitude late QRS signal found on the body surface in 5 pts. The last 40 msec of the QRS contained a higher proportion of fractionated electrograms (78 ± 22%) compared to the rest of the QRS (29 ± 14%, $p<.0001$). Slow conduction could not be detected on the body surface in 2 pts; 1 with left bundle branch block and 1 with brief fractionated electrograms which ended 80 msec after QRS onset.

Conclusion: A low level, high frequency, late QRS signal, which identifies pts with VT, originates from endocardial areas of slow conduction within the infarct zone.

ARRHYTHMOGENICITY OF ENCAINIDE. THE ROLE OF QT INTERVAL.

George B. Bren, MD; P. Jacob Varghese, MD, FACC; Richard J. Katz, MD; Allan M. Ross, MD, FACC; George Washington University, Washington, D.C.

Although Encainide (E) has been an effective agent for suppressing ventricular ectopy, recent reports suggest that some patients may become refractory to E or E may induce ventricular tachycardia (V.T.). Electrocardiograms (E.C.G.) of 8 patients (pts) (age 14-58 years) who were treated with E for refractory V.T. were reviewed to determine whether any of the E.C.G. measurements would be a predictor of continuing electrical instability.
None of the pts was taking any drug which would affect E.C.G. measurements, nor were there any electrolyte abnormalities during E therapy. In all pts P-R, QRS, and QTc intervals were measured before and after E.
In 4 pts (group A) QTc increased from 410 ± 50 msec. to 540 ± 60 msec. ($P < 0.02$) after E with minimum prolongation of 90 msec. In the other 4 pts (group B) QTc did not prolong after E (440 ± 50 to 440 ± 60). In both groups P-R and QRS intervals increased after E but neither measurement was significantly different between the two groups. Daily dose of E was not significantly different between the two groups: group A 262 mg. and group B 238 mg.
All pts in group A showed continuing electrical instability: exercise induced V.T. (2 pts), V.T. during repetitive ventricular stimulation (R.V.S.) (1 pt) and 1 pt had new spontaneous V.T. and V.T. induced by R.V.S. In contrast none of the group B had V.T. during exercise or R.V.S. These results indicate that arrhythmogenicity of E can be predicted by its effect on QTc independent of QRS effects of the drug.

THURSDAY, MARCH 19, 1981
AM
BIOPSY AND OTHER ASSESSMENTS OF CARDIAC DISEASE
10:30-12:00

QUANTIFICATION OF VALVULAR REGURGITATION BEFORE AND AFTER MEDICAL AND SURGICAL THERAPY BY RADIONUCLIDE ANGIOGRAPHY.

Joann Urquhart MD, Milton Packer MD, FACC, Randolph Patterson MD, FACC, Steven F. Horowitz MD, FACC, Ken Miceli RT , Richard Gorlin MD, FACC. Mount Sinai Medical Center, New York, N.Y.

A noninvasive method of quantifying valvular regurgitation (VR) to evaluate the results of medical and surgical therapy is needed. Radionuclide gated cardiac blood pool scans (GBPS) were performed in 42 patients (pts): group I (18 pts) had primary VR (aortic or mitral) with good LV function, group II (14 pts) had VR with poor LV function, and group III (10 pts) had no VR. VR was quantified by calculating a regurgitant ratio (RR) of LV to RV stroke counts (enddiastolic minus endsystolic counts in RV and LV regions of interest).

In group I pts, values for RR correlated closely (r=0.95) with measurements of regurgitant fraction derived from simultaneous determination of total and forward stroke volumes during cardiac catheterization. After valve replacement surgery, values for RR in these pts decreased (↓) from 4.03 ± 1.46 to 1.38 ± 0.23 ($p<.001$), a value similar to that observed in group III pts without VR (1.32 ± 0.15). All 3 pts with residual postoperative VR had RR values > 2SD above the mean values for group III (↓ 1.62); the remaining 15 pts without VR had smaller RR values.

In group II pts, treatment with oral hydralazine (H) increased stroke volume index (SVI)(20 to 38 cc/beat/m^2) and ↓ systemic vascular resistance (SVR) (2245 to 915 dynes-sec-cm-^{5}). Simultaneous GBPS showed no significant change in ejection fraction (EF) (.18 to .21) but values for RR ↓ from 3.37 ± 1.24 to 2.12 ± 0.79, $p< .001$. Changes in SVR and SVI with H correlated closely with changes in RR values (r=0.92 and 0.84, respectively) but not with changes in EF (r=0.15 and 0.18).

In conclusion, calculation of RR by GBPS is an accurate noninvasive method of quantifying VR before and after medical and surgical therapy.

PLATELET SURVIVAL TIME AND BETATHROMBOGLOBULIN IN CARDIAC VALVE REPLACEMENT

Alexander G.G. Turpie, M.D., Auke C. de Boer, M.D., Edward Genton, M.D., Rodney Butt, Ping Han, M.D., John Gunstensen, M.D., Hamilton General Hospital and McMaster University, Hamilton, Ontario, Canada.

Abnormal platelet survival time (PST) and betathromboglobulin (BTG) concentration have been reported to identify patients at risk of thromboembolism and to predict response to antithrombotic therapy after cardiac valve replacement. ^{51}Chromium - PST calculated by the exponential model (normal 118 hrs ± 16) and plasma BTG (normal 28 ng/ml ± 8) were measured pre and post replacement of the aortic (AVR, n=39) or mitral (MVR, n=64) valves. Urine BTG (normal 0.18 ng/ml ± 0.18) was measured after MVR. Mean PST pre and post AVR was similar to normal ($p>0.1$), but was reduced pre MVR (98 ± 26 $p<0.05$) and abnormal in 35%, became normal post MVR (109 ± 21) and remained reduced in 8% of patients. Plasma BTG was elevated pre (44 ± 25) and post (36 ± 15) AVR and pre (42 ± 25) and post (50 ± 43) MVR, $p<0.05$. Urine BTG was elevated post MVR (0.30 ± 0.22) and abnormal in 22% of patients. Urine but not plasma BTG concentration correlated with PST (r=-0.51, $p<0.05$). There was no difference in the results between tissue or prosthetic valves at either site. Abnormal platelet tests did not correlate with thromboembolism. BTG was abnormal pre and post AVR and MVR. PST was normal pre and post AVR and was abnormal pre-MVR but usually became normal post-MVR. Neither BTG nor PST have clinical value in the management of patients with valvular heart disease.

PLATELET REACTIVITY IN PATIENTS WITH AORTIC VALVE DISEASE

Jeanne M. Riddle, PhD, Paul D. Stein, MD, FACC, Henry Ford Hospital, Detroit, Michigan

Platelet reactivity was evaluated in 30 patients who required replacement of their aortic valve: 16 had predominant aortic stenosis (AS) and 14 had predominant aortic insufficiency (AI). Electron microscopy was used to determine the amount of cytoplasmic spreading by single platelets and the amount of aggregation that resulted from exposure to a Formvar film in vitro. A hyperactive response was defined as >20% spread type platelets with decreased numbers of dendritic forms and/or increased aggregates (>93 aggregates/100 single platelets). Such platelet reactivity occurred in only 8% (6 of 72) of normal subjects; whereas in patients with aortic valve disease, 60% (18 of 30) showed a hyperactive platelet response ($P < .01$). The number of patients with AS who had hyperactive platelets, 69% (11 of 16) was comparable to the number with AI, 50% (7 of 14) (NS). Patients both with AS and AI had more hyperactive platelets than normal subjects ($P < .01$). The occurrence of hyperactive platelets in patients with AS and AI is compatible with the previous observation of platelet deposition on stenotic valves removed at surgery. Turbulence, high shear stresses, and exposed abnormal surfaces may contribute to the increased platelet reactivity.

ENDOMYOCARDIAL BIOPSY IN PATIENTS WITH LIFE-THREATENING VENTRICULAR DYSRHYTHMIA

Guy S. Reeder, MD; David R. Holmes, MD; Geoffrey O. Hartzler, MD; William D. Edwards, MD; Mayo Clinic and Foundation, Rochester, MN

Patients with "primary" myocardial disease may initially present with cardiovascular collapse due to ventricular tachycardia (VT) or fibrillation (VF). Long term management of survivors might be improved by knowledge of underlying myocardial pathology. To evaluate this, 17 patients (9 males, 8 females, mean age 27 years) underwent endomyocardial biopsy as part of comprehensive evaluation of unheralded VT (10 patients) or VF (7 patients). Coronary arteriography disclosed no obstructive lesion in any patient.

Biopsy results showed that 9 patients (53%) had findings suggesting early cardiomyopathy with prominent interstitial fibrosis, cellular hypertrophy or atrophy. These patients received antiarrhythmic therapy. Five patients (29%) had findings of myocarditis with lymphocytic infiltration and interstitial edema. Four of these patients received steroid therapy; three showed complete resolution of inflammatory changes on serial biopsy, however, in 2 of these 3 patients persistence of dysrhythmia required specific antiarrhythmic drug therapy. Three patients (18%) had normal biopsy findings - one patient in this group had mitral prolapse and another had long QT interval.

We conclude 1) endomyocardial biopsy is helpful in defining underlying pathology in this heterogenous patient population, 2) biopsy is often helpful in selecting appropriate drug therapy especially in patients with unsuspected myocarditis. Further experience is required to determine if biopsy may be used to prognosticate survival or clinical course.

MYOCARDIAL BIOPSY IN PATIENTS WITH VENTRICULAR TACHYCARDIA

Diederik van Hoogenhuyze, MD; Eckhardt Olsen, MD, F.R.C. Path.; Berry Crook, M.R.C.P.; Marcel van de Brand, MD. Zuiderziekenhuis, Rotterdam, The Netherlands.

In most patients(pts) with ventricular tachycardia (VT), an underlying cardiac abnormality can be demonstrated. In some however, extensive investigation does not reveal an apparent cardiac cause. To assess the diagnostic role of myocardial biopsy, multiple(2-7, mean 3.2) endomyocardial catheter biopsies from the RV and/or LV were obtained in 15 pts,(mean age 31,2 yrs, range 21-54). They presented with symptomatic ventricular dysrythmias, and recurrent VT was demonstrated in all by routine ECG or ambulatory monitoring. Only 4 pts had cardiomegaly or signs of heart failure. With clinical examination, non-invasive testing(including echocardiography and exercise test), and right and left heart catheterisation, congenital, valvular and coronary heart disease could be ruled out. LV volume was increased and ejection fraction decreased in 5 pts; the 10 remaining had normal LV function. Coronary angiograms were all normal. Microscopic evaluation of the biopsies was compatible with congestive cardiomyopathy in 9 pts, of whom 6 had normal LV function. Diagnosis was based on a combination of hypertrophied muscle fibers, increased interstitial fibrosis and endocardial thickening. Chronic myocarditis was diagnosed in 4 cases; one biopsy showed extensive fibrosis of unknown etiology and 1 was normal.

Conclusion: 1.Fourteen out of 15 pts, presenting with clinically unexplained VT, had abnormal biopsy findings. 2.The majority of the abnormal biopsies were compatible with a diagnosis of congestive cardiomyopathy. 3.Ventricular dysrythmias may be an indication of congestive cardiomyopathy even in the absence of cardiac enlargement or abnormal function.

THE USE OF TRANSVENOUS MYOCARDIAL BIOPSY TO DIAGNOSE AND ACCURATELY EVALUATE DISEASES OF THE MYOCARDIUM

Joseph E. Parrillo, MD; Thomas Aretz, MD; Igor Palacios, MD; John T. Fallon, MD and Peter C. Block, MD, FACC, Massachusetts General Hospital, Boston, Massachusetts

Transvenous myocardial biopsy (TMB) has been shown to be diagnostically helpful in cardiac transplant rejection, however it has been debated whatever it is useful in evaluating other cardiac diseases. Since 1975, 49 TMBs have been performed at Massachusetts General Hospital to help evaluate a variety of patient with myocardial diseases. Adequate biopsy material was obtained in all 49 patients, and there were no major or minor complications. The TMB was judged as definitely helpful to the clinician in 24 (49%) and probably helpful in an additional 16 (33%) patients. A definitive pathologic diagnosis was made in 16 (33%), and a confirmatory pathologic diagnosis was made in an additional 13 (27%) patients. The TMB pathologic diagnosis was confirmed in 7 or 7 (100%) patients who came to autopsy or surgery. TMB identified several potentially specifically treatable myocardial disease: myocarditis (6 pts.), vasculitis (1 pt.), hypereosinophilic cardiomyopathy (2 pts.), and radiation-induced cardiomyopathy (2 pts.). In 4 of 6 patients with biopsy-demonstrated myocarditis, the clinical picture was not typical of myocarditis and the diagnosis would have been missed if TMB had not been performed. In 15 patients with constrictive/restrictive physiology, TMB was found to be very useful and accurate in differentiating restrictive cardiomyopathy from constrictive pericarditis. When a complete clinical evaluation was combined with TMB, TMB provided diagnostic information that was very frequently of major help to the clinician (definitely or probably helpful in 82%) in the evaluation of a variety of myocardial diseases.

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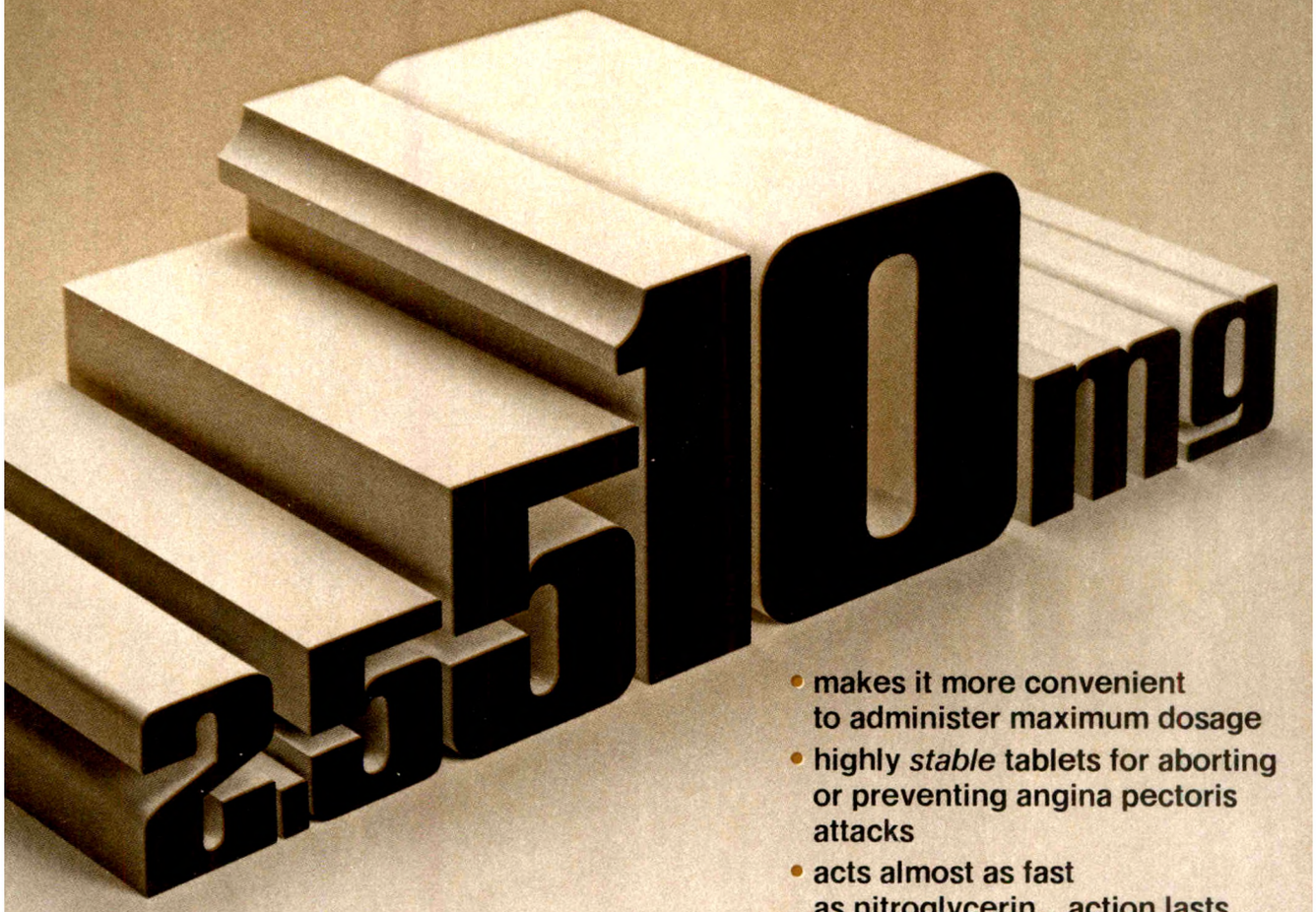

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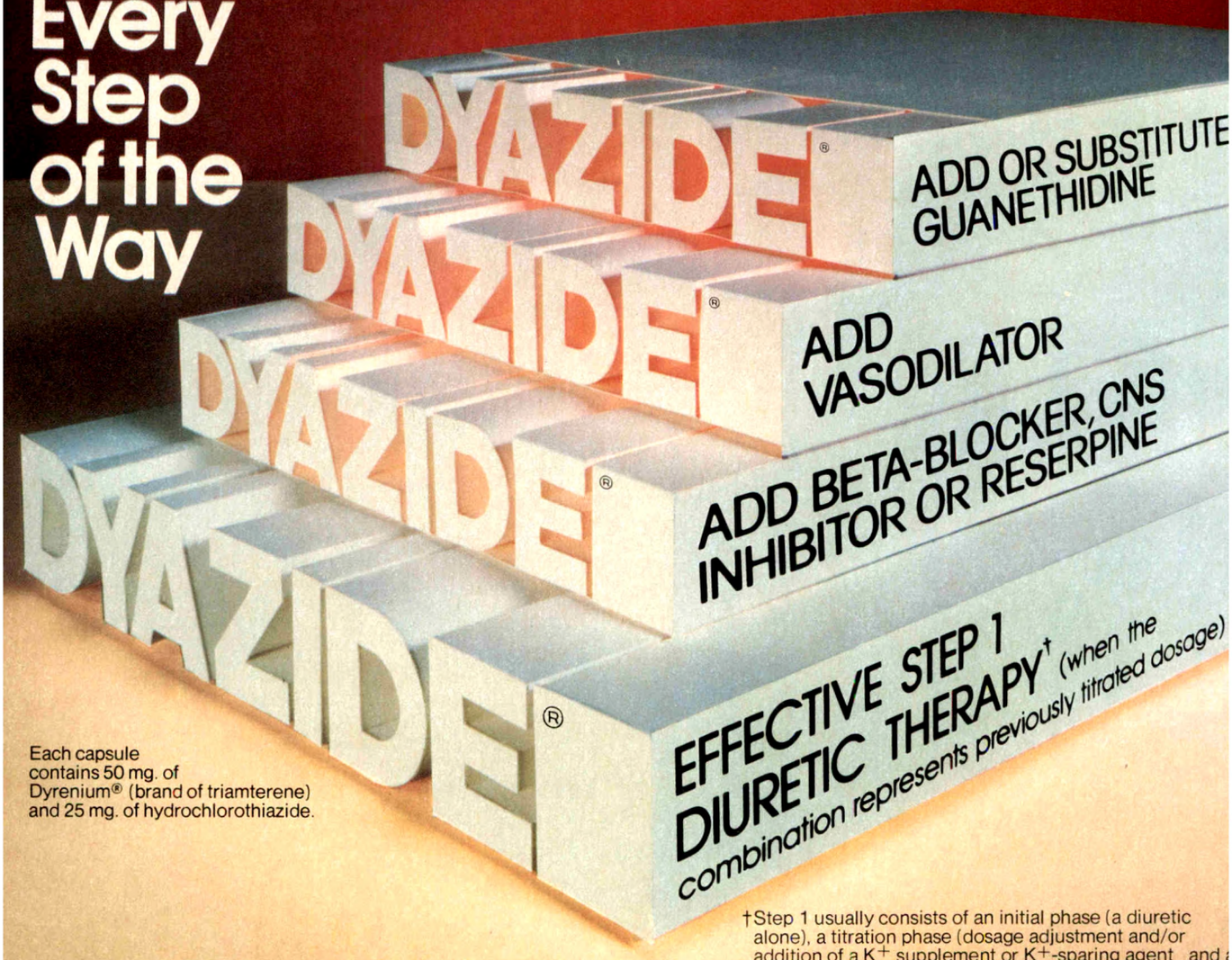

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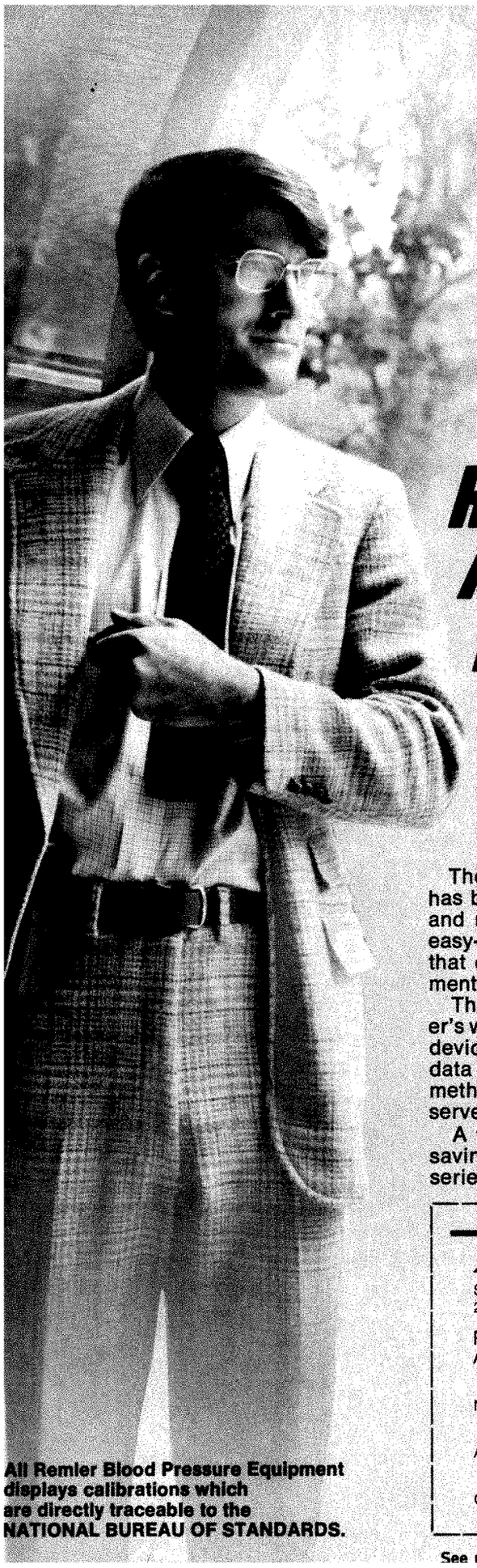

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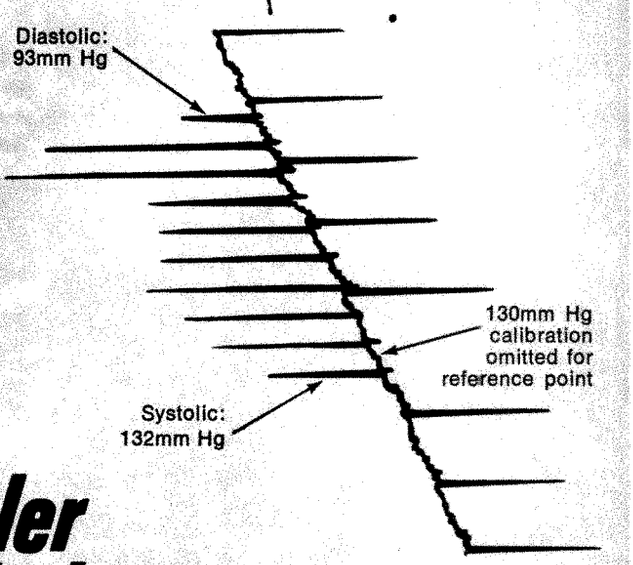

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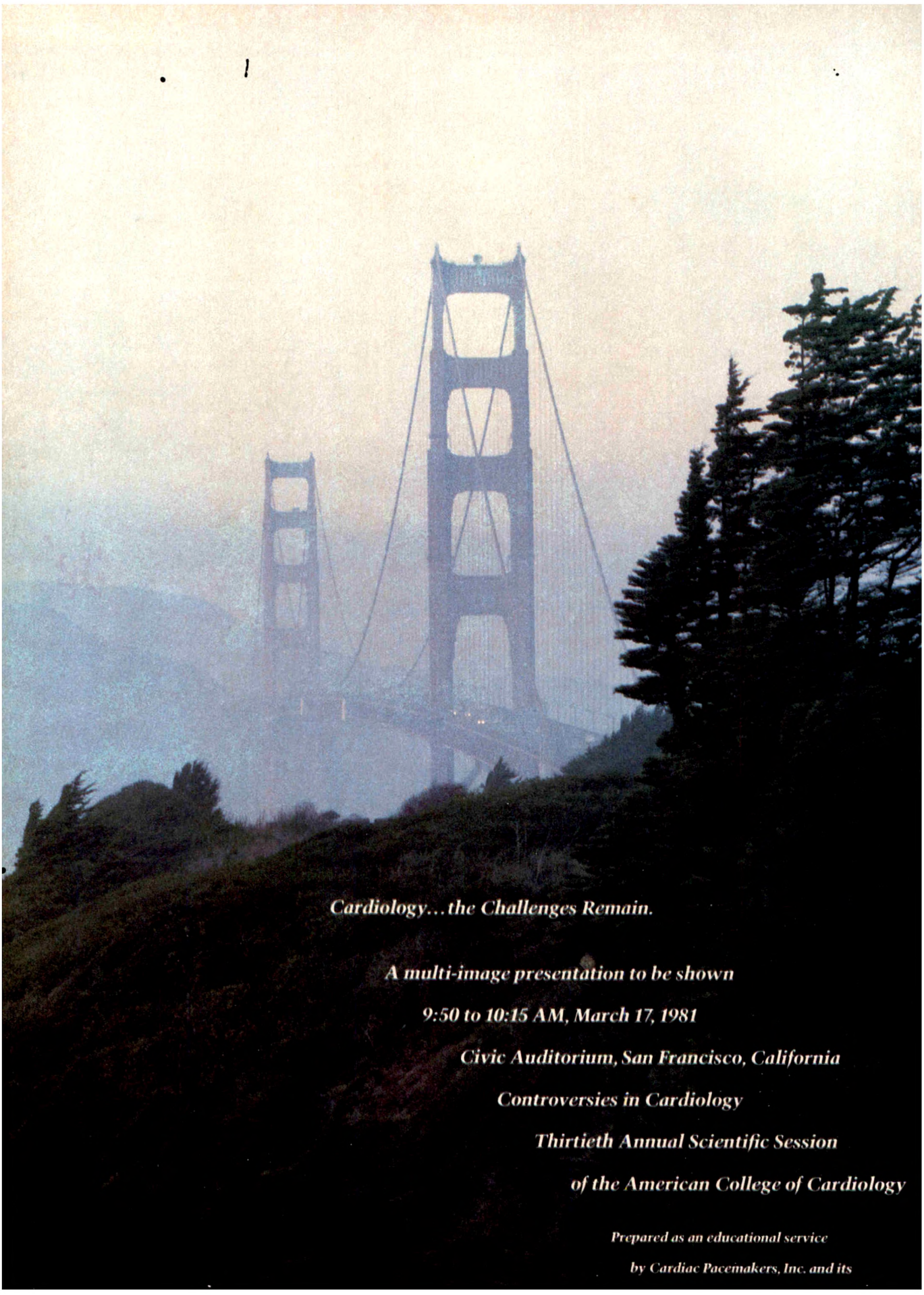
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Hersey Professor of the Theory and Practice of Medicine
Harvard Medical School

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■ Moderator's Introduction	**Eugene Braunwald, M.D., F.A.C.C.**
■ Calcium Channel Blockers: A New Concept in Cardiologic Treatment	**Dennis Krikler, M.D., F.A.C.C.** *Consultant Cardiologist* *Royal Postgraduate Medical School* *Hammersmith Hospital, London, England*
■ Electrophysiological Properties of Different Calcium Channel Blockers	**William J. McKenna, M.D.** *Senior Research Fellow* *Royal Postgraduate Medical School* *Hammersmith Hospital, London, England*
■ Nifedipine in Chronic Stable Angina	**Henry Dargie, M.B., M.R.C.P.** *Consultant Cardiologist* *Western Infirmary* *Glasgow, Scotland*
■ Nifedipine in Unstable Angina	**Paul G. Hugenholtz, M.D., F.A.C.C.** *Professor of Cardiology* *Erasmus University* *Rotterdam, Holland*
■ Nifedipine: Beneficial Enhancement of Coronary Flow	**Heinz-Jürgen Engel, M.D.** *Senior Lecturer in Cardiology* *University of Hanover Medical School* *Hanover, Germany*

ROUNDTABLE DISCUSSION

Nifedipine: A Discussion of European and American Experienc

MODERATOR: **Dennis Krikler, M.D., F.A.C.C.**

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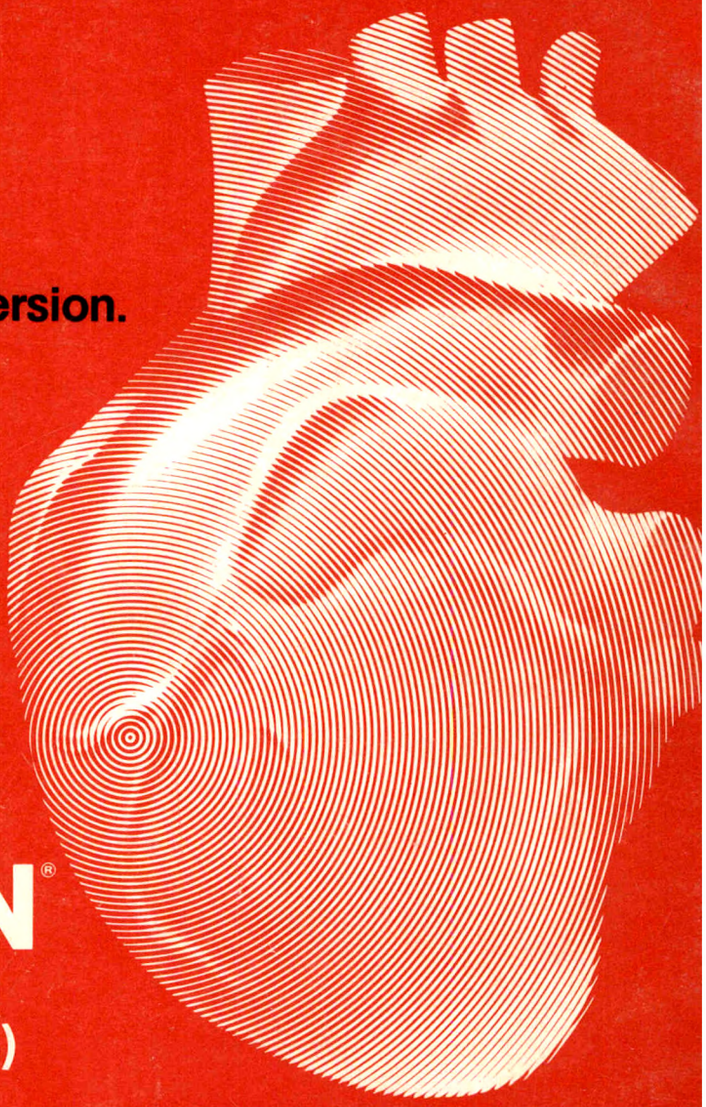

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*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

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Eleventh Bethesda Conference:
Prevention of Coronary Heart Disease

Seminar on Cardiovascular Function in Respiratory Failure—I

Richard A. Matthay, MD and Lawrence D. H. Wood, MD, Guest Editors

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Will an antihypertensive generally allow a normal cardiovascular response to exercise?

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In a recent study of hypertensive patients whose cardiovascular response to exercise was evaluated before and during methyldopa therapy, "...methyldopa significantly reduced the rise in systolic pressure during the build-up ($P<0.01$) and subjective maximal stages ($P<0.05$) as well as at all phases of recovery ($P<0.01$)." Moreover, "The total duration of exercise (an index of work capacity) was unchanged with...methyldopa."[3]

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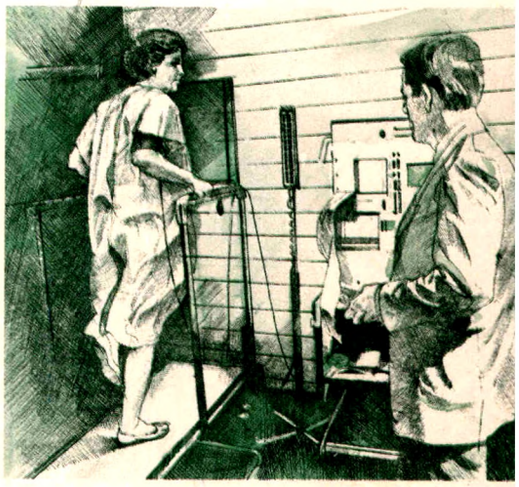
- Has documented long-term efficacy.
- Significant adverse effects have been infrequent and the agent is usually well tolerated.



ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if prev methyldopa therapy has been associated with l disorders. It is important to recognize that a pos Coombs test, hemolytic anemia, and liver disor may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disord could lead to potentially fatal complications unl properly recognized and managed.

1. Yasky J, Carosella C, Costa O: Diagnosis of arterial hype tension by means of a graduated ergometric test, in Zanch (ed): ALDOMET® (Methyldopa | MSD) in Worldwide Cli Experience, West Point, PA, Merck Sharp & Dohme, 197 pp 56-63.
2. Mancia G, Ferrari A, Gregorini G, et al: Effects of treat with methyldopa on basal hemodynamics and on neural c latory control, in Zanchetti A (ed): ALDOMET® (Methyl MSD) in Worldwide Clinical Experience, West Point, PA, Merck Sharp & Dohme, 1979, pp 27-39.
3. Lee WR, Fox LM, Slotkoff LM: Effects of antihypertensi therapy on cardiovascular response to exercise. Am J Car 44:325-328, 1979.

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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, occasionally with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Pregnancy and Nursing: Use of any drug in women who are or may become pregnant or intend to nurse requires that anticipated benefits be weighed against possible risks; possibility of fetal injury or injury to a nursing infant cannot be excluded. Methyldopa crosses the placental barrier, appears in cord blood, and appears in breast milk.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: urinary uric acid by the phosphotungstate method, serum creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced
anesthetics; hypotension occurring durir
thesia usually can be controlled with vasop
Hypertension has recurred after dialysis in
on methyldopa because the drug is remove
procedure.

Adverse Reactions: *Central nervous syster*
tion, headache, asthenia or weakness, usu
and transient; dizziness, lightheadedness
toms of cerebrovascular insufficiency, pare
parkinsonism, Bell's palsy, decreased ment
involuntary choreoathetotic movements;
disturbances, including nightmares and r
mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation
pectoris. Orthostatic hypotension (decrea
dosage). Edema (and weight gain) usually re
use of a diuretic. (Discontinue methyldopa
progresses or signs of heart failure appear.

Gastrointestinal: Nausea, vomiting, distenti
stipation, flatus, diarrhea, mild dryness o
sore or "black" tongue, pancreatitis, sialad

Hepatic: Abnormal liver function tests, j
liver disorders.

Hematologic: Positive Coombs test, hemol
mia. Leukopenia, granulocytopenia, thron
penia. Positive tests for antinuclear antib
cells, and rheumatoid factor.

Allergic: Drug-related fever, lupus-like sy
myocarditis.

Other: Nasal stuffiness, rise in BUN, breast
ment, gynecomastia, lactation, impoter
creased libido, dermatologic reactions i
eczema and lichenoid eruptions, mild ar
myalgia.

Note: Initial adult dosage should be lir
500 mg daily when given with antihyper
other than thiazides. Tolerance may occur,
between second and third months of
increased dosage or adding a diuretic fr
restores effective control. Patients with i
renal function may respond to smaller
Syncope in older patients may be related to ir
sensitivity and advanced arteriosclerotic
disease; this may be avoided by lower dose

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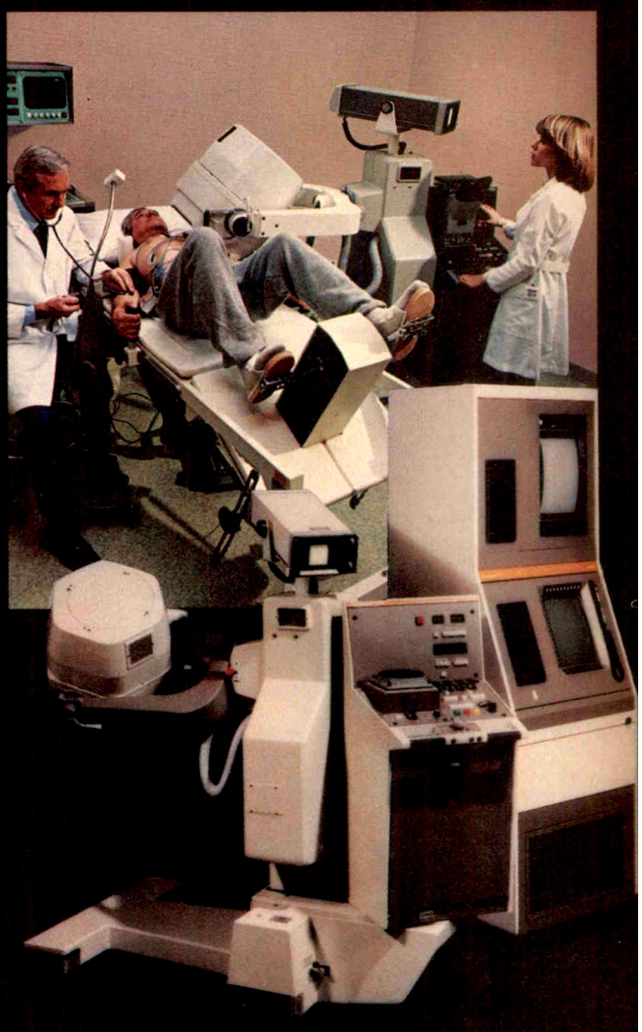

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In Hypertension*...When You Need to Conserve K^+

Every Step of the Way

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

†Step 1 usually consists of an initial phase (a diuretic alone), a titration phase (dosage adjustment and/or addition of a K^+ supplement or K^+-sparing agent and a maintenance phase (a diuretic alone or in combination with a K^+ supplement or K^+-sparing agent).

Serum K^+ and BUN should be checked periodically (see Warnings).

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia, although uncommon, has been reported. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components.

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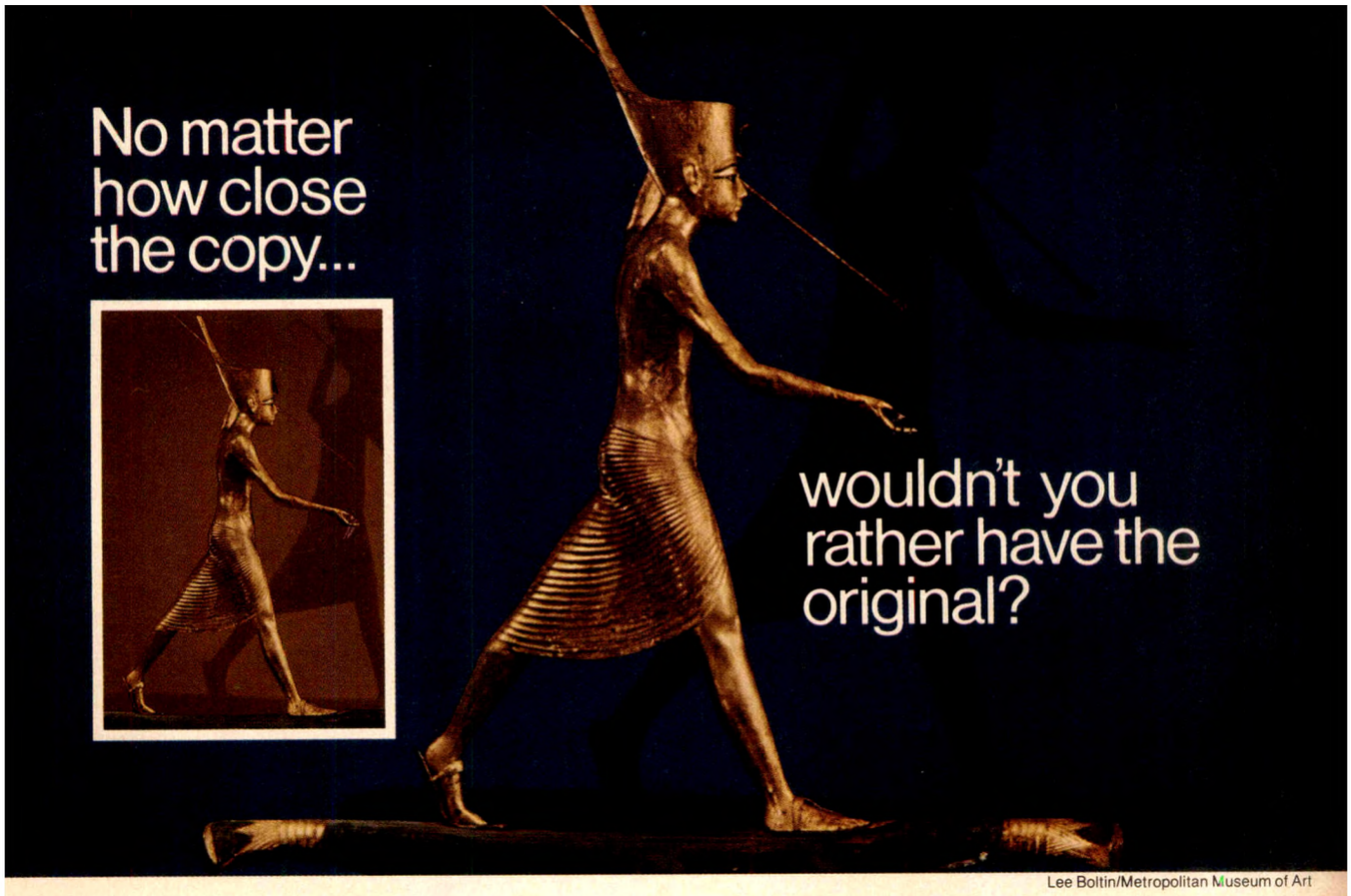

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INDICATIONS—Based on a review of this drug by the National Academy of Science-National Research Council and /or other information, FDA has classified the indication as follows:

"Possibly" effective: For long-term therapy of chronic angina pectoris. Prolonged therapy may reduce the frequency or eliminate anginal episodes, improve exercise tolerance, and reduce nitroglycerin requirements. The drug is not intended to abort the acute anginal attack.

Final classification of the less-than-effective indications requires further investigation.

CONTRAINDICATIONS—No specific contraindications are known.

PRECAUTIONS—Since excessive doses can produce peripheral vasodilation, the drug should be used cautiously in patients with hypotension. Persantine tablets, 25 mg, contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. The incidence of sensitivity is generally low, but frequently seen in patients with aspirin hypersensitivity.

ADVERSE REACTIONS— Adverse reactions are minimal and transient at recommended dosages. Instances of headache, dizziness, nausea, flushing, weakness or syncope, mild gastrointestinal distress and skin rash have been noted during therapy. Rare cases of what appeared to be an aggravation of angina pectoris have been reported, usually at the initiation of therapy. On those uncommon occasions when adverse reactions have been persistent or intolerable, withdrawal of medication has been followed promptly by cessation of undesirable symptoms.

DOSAGE AND ADMINISTRATION—The recommended dosage is 50 mg three times a day, taken at least one hour before meals. In some cases higher doses may be necessary but a significantly increased incidence of side effects is associated with increased dosage. Clinical response may not be evident before the second or third month of continuous therapy.

Tablets of 25 mg and 75 mg

For complete details, please see the full prescribing information.

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Please see brief summary of prescribing information on adjoining page.

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26790 A

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Klorvess® Effervescent Granules and Klorvess® (potassium chloride) 10% Liquid

Brief summary of prescribing information

DESCRIPTION: *Klorvess Effervescent Granules:* Each packet (2.8 g) contains 20 mEq each of potassium and chloride supplied by potassium chloride 1.125 g, potassium bicarbonate 0.5 g, L-lysine monohydrochloride 0.913 g in a sodium-, sugar- and carbohydrate-free effervescent formulation. Dissolution of the packet contents in water provides the potassium and chloride available for oral ingestion as potassium chloride, potassium bicarbonate, potassium citrate and L-lysine monohydrochloride.

Klorvess (potassium chloride) 10% Liquid: Each tablespoonful (15 ml) contains 20 mEq of potassium chloride (provided by potassium chloride 1.5 g) in a palatable, cherry-with-pit flavored vehicle, alcohol 1%.

INDICATIONS: For the prevention and treatment of potassium depletion and hypokalemic-hypochloremic alkalosis. Deficits of body potassium and chloride can occur as a consequence of therapy with potent diuretic agents and adrenal corticosteroids.

CONTRAINDICATIONS: Severe renal impairment characterized by azotemia or oliguria, untreated Addison's disease, Familial Periodic Paralysis, acute dehydration, heat cramps, patients receiving aldosterone-inhibiting or potassium-sparing diuretic agents, or hyperkalemia from any cause.

PRECAUTIONS: In response to a rise in the concentration of body potassium, renal excretion of the ion is increased. In the presence of normal renal function and hydration, it is difficult to produce potassium intoxication by oral potassium salt supplements. Since the extent of potassium deficiency cannot be accurately determined, it is prudent to proceed cautiously in undertaking potassium replacement. Periodic evaluations of the patient's clinical status, serum electrolytes and the EKG should be carried out when replacement therapy is undertaken. This is particularly important in patients with cardiac disease and those patients receiving digitalis. High serum concentrations of potassium may cause death through cardiac depression, arrhythmia or cardiac arrest. To minimize gastrointestinal irritation associated with potassium chloride preparations, patients should dissolve the packet contents of *Klorvess Effervescent Granules* in 3 to 4 ounces of cold water, fruit juice or other liquid or dilute each tablespoonful of *Klorvess (potassium chloride) 10% Liquid* in 3 to 4 ounces of cold water. Both of these solutions should be ingested slowly with or immediately after meals.

ADVERSE REACTIONS: Abdominal discomfort, diarrhea, nausea and vomiting may occur with the use of potassium salts. The symptoms and signs of potassium intoxication include paresthesias, heaviness, muscle weakness and flaccid paralysis of the extremities. Potassium intoxication can produce listlessness, mental confusion, a fall in blood pressure, shock, cardiac arrhythmias, heart block and cardiac arrest. The EKG picture of hyperkalemia is characterized by the early appearance of tall, peaked T waves. The R wave is decreased in amplitude and the S wave deepens; the QRS complex widens progressively. The P wave widens and decreases in amplitude until it disappears. Occasionally, an apparent elevation of the RS-T junction and a cove plane RS-T segment and T wave will be noted in AVL.

DOSAGE AND ADMINISTRATION: *Klorvess Effervescent Granules:* Adults—One packet completely dissolved 2 to 4 times daily depending upon the requirements of the patient.

Klorvess (potassium chloride) 10% Liquid: Adults—One tablespoonful (15 ml) completely diluted in cold water 2 to 4 times daily depending upon the requirements of the patient.

Both of these solutions should be ingested slowly with meals or immediately after eating.

OVERDOSAGE: Potassium intoxication may result from overdosage of potassium or from therapeutic dosage in conditions stated under "Contraindications." Hyperkalemia, when detected, must be treated immediately because lethal levels can be reached in a few hours. In digitalized patients too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

HOW SUPPLIED: *Klorvess Effervescent Granules*—packages of 30 packets (2.8 g each). *Klorvess (potassium chloride) 10% Liquid* (dark red)—as a cherry-with-pit flavored liquid in pint and gallon bottles. Klorvess Effervescent Granules and Liquid are also available in institutional packaging as follows: *Klorvess Effervescent Granules*—packages of 1000 packets; *Klorvess Liquid*—36 (3 x 12) x 4 oz Unit-of-Use bottles and 100 (4 x 25) x 15 ml Unit-Dose bottles.

(For complete details, please consult full prescribing information)

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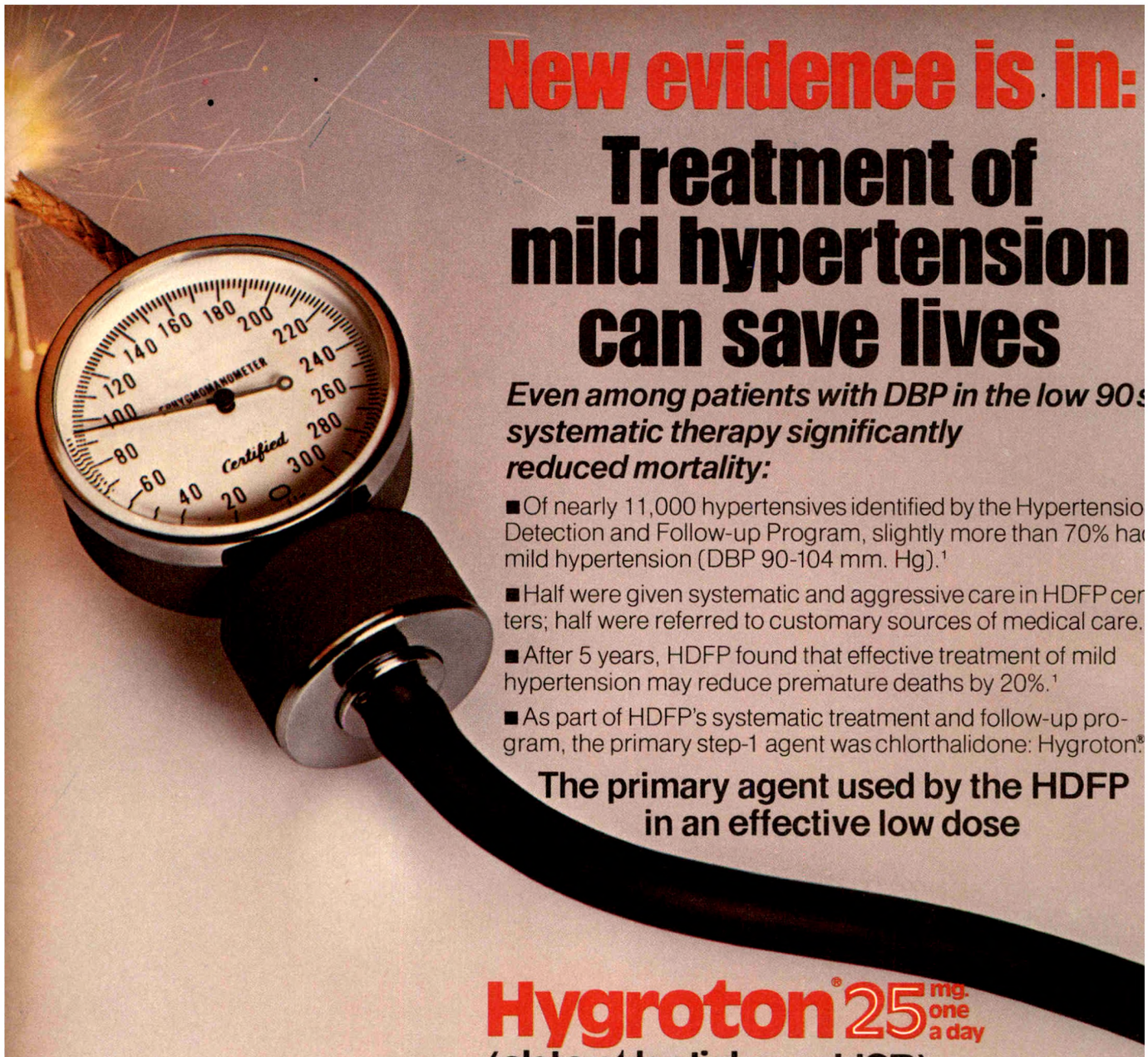

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- After 5 years, HDFP found that effective treatment of mild hypertension may reduce premature deaths by 20%.[1]
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(chlorthalidone USP)

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BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs. **Warnings:** Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. There is a possibility of exacerbation or activation of systemic lupus erythematosus with thiazides, which are related to chlorthalidone. This has not been reported with chlorthalidone. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing. **Precautions:** Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis; dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored), 50 mg. (aqua) in bottles of 100, 1000 and 5000; 25 mg. (peach) in bottles of 100 and 1000; unit-dose blister packs, boxes of 100 (10 x 10 strips).

References:
1. Five-year Findings of the Hypertension Detection and Follow-up Program: 1. Reduction in Mortality of Persons With High Blood Pressure, Including Mild Hypertension, JAMA 242: 2562, Dec. 7, 1979. 2. Payne, G.H.: Presentation of HDFP findings (Nov. 27, 1979), data on file, USV Laboratories.

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CLINICAL STUDIES

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VALENTIN FUSTER, BERNARD J. GERSH, EMILIO R. GIULIANI, ABDUL J. TAJIK, ROBERT O. BRANDENBURG and ROBERT L. FRYE

This long-term retrospective follow-up study of 104 patients with idiopathic dilated cardiomyopathy reveals that age, cardiothoracic ratio on chest X-ray film and cardiac index are highly predictive of the clinical course. The combination of cardiac index and cardiothoracic ratio permitted 86 percent of the patients to be correctly classified with respect to 3 year survival. Twenty-four patients (23 percent) in this series survived. The occurrence of systemic emboli in 18 percent of patients who did not receive anticoagulant therapy and in none who received such therapy suggests that anticoagulant drugs should be used in this condition unless they are contraindicated. In the genesis of this condition possible etiologic risk factors of infectious-immunologic type may be important.

532 Prognosis in Hypertrophic Cardiomyopathy: Role of Age and Clinical, Electrocardiographic and Hemodynamic Features

WILLIAM McKENNA, JOHN DEANFIELD, AZHAR FARUQUI, DIANE ENGLAND, CELIA OAKLEY and JOHN GOODWIN

The history at the time of diagnosis and changes in symptoms during follow-up proved better predictors of poor prognosis than electrocardiographic or hemodynamic measurements in this retrospective study of the clinical course of 254 patients with hypertrophic cardiomyopathy. The combination of young age, syncope at diagnosis, severe dyspnea at last follow-up and a family history of hypertrophic cardiomyopathy and sudden death best predicted sudden death. Mainly because of the high overall operative mortality rate (27 percent) the total 6 year mortality rate for surgically treated patients exceeded that of the medically treated ones. In this series 55 percent of the deaths were sudden and associated with a previous history of syncope. Ventricular arrhythmia is probably the antecedent event in most sudden deaths. Traditional treatment with beta receptor blocking drugs and the newer treatment with verapamil are effective against ventricular arrhythmias in hypertrophic cardiomyopathy.

539 Comparison of Coronary Arteriographic Findings During Angina Pectoris Associated With S-T Elevation or Depression

HIROFUMI YASUE, SHINGO OMOTE, AKINORI TAKIZAWA, NAGAO MASAO, HIROMITSU HYON, SHINICHIRO NISHIDA and MINORU HORIE

Coronary arteriographic studies during 64 attacks of induced or spontaneous angina pectoris indicate that angina pectoris associated with S-T segment elevation usually indicates more severe myocardial ischemia than angina associated with S-T segment depression. The former represents transmural ischemia and the latter subendocardial ischemia. The majority (76.3 percent) of the attacks with S-T elevation were associated with total occlusion of a major coronary artery. Spasm of an artery supplying an area of myocardium represented by S-T segment shift in the electrocardiogram appeared during an attack of angina, and disappeared with subsidence of the attack after nitroglycerin administration in all 38 attacks associated with S-T segment elevation and in 22 of the 26 attacks associated with S-T depression. The majority (76.9 percent) of angina attacks associated with S-T segment depression were accompanied by either subtotal spastic occlusion or diffuse narrowing of a major coronary artery.

Continued on page A16

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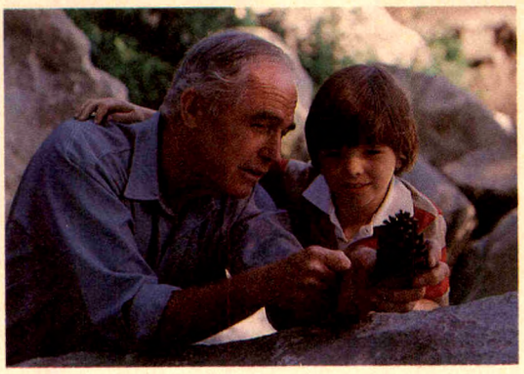
For AV pacing in most patients, one thin, slippery Spectraflex lead is easily passed in the same vein with one of our new urethane atrial leads.

In both AV and ventricular pacing, you can expect superior performance from Spectraflex leads. They are designed for better electrical efficiency, less likelihood of fracture and, of course, stability because of the proven effectiveness of their tines. The urethane-wrapped DBS (drawn brazed strand) coil conductors offer five times the flex life of older style leads. And the ring-tip electrode provides efficient sensing and stimulation thresholds while minimizing tissue trauma.

Only Medtronic's proven, reliable technology could make these bold steps possible. And we'll keep setting the standards for leads, pacemakers and pacing support, to help you give your patients a firmer hold on life.



Medtronic

Leading the way to man's heart.

A13

MEDTRONIC PRODUCT INFORMATION SUMMARY

Medtronic Implantable Pacing Leads and Accessories

Intended Use–

Medtronic implantable pacing leads and accessories are designed to be used with Medtronic pulse generators as part of a cardiac pacing system (see product labeling for specific directions regarding applications).

Contraindications–

Endocardial pacing leads are contraindicated in the presence of tricuspid valvular disease.

Myocardial leads are contraindicated for a patient whose myocardium is thin-walled, suffused with fat or infarcted in the area of electrode placement.

Myocardial leads may be contraindicated in the older high-risk patients with a low tolerance to general anesthesia.

Use of the introducer is contraindicated if the patient has a known or suspected obstruction in the subclavian vein. There is increased risk of pneumothorax. Poor healing may result in the patient who has had irradiation to the anterior chest.

Temporary leads are contraindicated for a patient whose myocardium is thin-walled, suffused with fat, or infarcted in the area of electrode placement.

Warnings–

An implanted lead or lead/adaptor combination constitutes a direct, low-resistance current path to the myocardium. During the connection and testing procedures, only battery-powered pulse generators should be used with the lead system to protect against ventricular fibrillation induced by alternating current leakage. Extreme caution must be taken to properly ground all line-powered equipment used in the vicinity of the patient.

Lead adaptors, lead extenders and repair kits should not be used if the integrity of the lead is in doubt.

Precautions–

The pacing system may cease to function due to lead-related problems such as displacement, fracture, fibrotic tissue formation and elevated thresholds.

Side Effects–

Body rejection phenomena, infection, erosion or migration through body tissue, transvenous lead-related thrombosis, embolism.

How Supplied–

Medtronic permanent implantable leads and accessories are supplied sterilized and, in most cases, individually packaged.

In chronic CHF . . . physiologically consistent with the disease state and its therapy

Aldactone®
(spironolactone 25 mg)

WARNING

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats (see Warnings). Aldactone should be used only in those conditions described under Indications. Unnecessary use of this drug should be avoided.

INDICATIONS: *Diagnosis and treatment of primary hyperaldosteronism. Essential hypertension, edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate. Cirrhosis of the liver accompanied by edema and/or ascites. Hypokalemia.* ***CONTRAINDICATIONS:*** *Anuria, acute renal insufficiency, significant impairment of renal function, or hyperkalemia.* ***WARNINGS:*** *Excessive potassium intake may cause hyperkalemia. Potassium supplements should not be given with Aldactone. Do not administer concurrently with other potassium-sparing diuretics. Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75, and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocytomegaly, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.* ***PRECAUTIONS:*** *Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Reversible hyperchloremic metabolic acidosis may occur in some patients with decompensated hepatic cirrhosis. Hyponatremia may be caused or aggravated, especially when Aldactone is administered in combination with other diuretics. Transient elevation of BUN and/or mild acidosis may occur. Aldactone potentiates the effect of other diuretics or antihypertensive agents, particularly ganglionic blocking agents; therefore the dosage of such drugs should be reduced by at least 50 percent when adding Aldactone. Gynecomastia may develop and in rare instances some breast enlargement may persist. Vascular responsiveness to norepinephrine may be reduced. Spironolactone may cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazard to the fetus. Breast feeding should be discontinued when Aldactone is being used.* ***ADVERSE REACTIONS:*** *Gynecomastia is observed not infrequently. Gastrointestinal symptoms including cramping and diarrhea, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established. Adverse reactions are usually reversible upon discontinuation of the drug.* ***DOSAGE AND ADMINISTRATION: For primary hyperaldosteronism:*** *400 mg. daily for three to four weeks (long test), or for four days (short test). For preparation for surgery or for long-term maintenance therapy, 100 to 400 mg. daily.* ***For edema in adults:*** *Initial daily dosage is 100 mg. in divided doses but may range from 25 to 200 mg. daily. If after five days an adequate diuretic response has not occurred, a second diuretic which acts more proximally in the renal tubule may be added. The dosage of Aldactone should remain unchanged when other diuretic therapy is added.* ***For edema in children:*** *Initial daily dosage should provide approximately 1.5 mg. per pound of body weight (3.3 mg./kg.) in divided doses.* ***For essential hypertension:*** *Initial adult daily dosage of 50 to 100 mg. in divided doses, alone or with diuretics which act more proximally in the renal tubule, or with other antihypertensive agents. Continue treatment for at least two weeks since maximal response may not occur before this time. Adjust subsequent dosage according to patient response.* ***For hypokalemia:*** *25 to 100 mg. daily in divided doses.*

SEARLE Searle & Co.
San Juan, PR 00936

Address medical inquiries to: G. D. Searle & Co., Medical Communications Department, Box 5110, Chicago, Illinois 60680

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In chronic CHF . . . when other measures are inadequate or considered inappropriate

Physiologically consistent with the disease state and its therapy

Aldactone®

(spironolactone 25 mg)

the "uncomplicator"

Effective and sustained diuresis

Aldactone, acting primarily at site IV in the distal convoluted tubule, competitively blocks the action of aldosterone. Aldactone thus promotes the excretion of sodium and water while it spares potassium.

Combats secondary volume buildup

The action of Aldactone is distinct from other potassium-sparing diuretics. Because it specifically antagonizes aldosterone, secondary volume buildup is mitigated, while edema and congestion are relieved.

Unique potassium-regulating effect

The unique potassium-regulating mechanism of Aldactone can prevent hypokalemia, with limited risk of hyperkalemia. Such side effects of conventional diuretics as hypokalemic alkalosis, digitalis toxicity, and cardiac arrhythmias are unlikely to occur. Consult Aldactone prescribing information for the side effects of spironolactone.

Limitations to consider

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. Thus, Aldactone should be prescribed only when other measures are considered inadequate or inappropriate. (See boxed warning and Warnings *section of Aldactone prescribing information.)*

SEARLE

Before prescribing, please consult the complete prescribing information, a brief summary of which appears on the facing page.

547 Coronary Flow Studies in Patients With Left Ventricular Hypertrophy of the Hypertensive Type. Evidence for an Impaired Coronary Vascular Reserve

AUGUSTO D. PICHARD, RICHARD GORLIN, HARRY SMITH, JOHN AMBROSE and JOSE MELLER with the technical assistance of WILLIAM KING and ONDINA BOBADILLA

Analysis of the hyperemic reaction to the selective injection of contrast agent into the coronary arteries of 25 patients with aortic stenosis and left ventricular hypertrophy indicates that there is a reduction in coronary vascular reserve related to the ischemic component of their hypertrophic heart disease. The decreased coronary vascular reserve was proportional to the increase in left ventricular mass and the decreased left ventricular-aortic diastolic gradient and aortic diastolic pressure. The clinical deterioration of patients with left ventricular hypertrophy secondary to aortic stenosis may well be related to left ventricular failure secondary to acute or chronic ischemia.

555 Assessment of Left Ventricular Function by Radionuclide Angiography During Induced Supraventricular Tachycardia

STEVEN SWIRYN, DAN PAVEL, ERNEST BYROM, CHRISTOPHER WYNDHAM, RAYMOND PIETRAS, ROBERT BAUERNFEIND and KENNETH M. ROSEN

Electrocardiographically synchronized radionuclide angiography performed before, during and after induced paroxysmal supraventricular tachycardia in 13 patients showed that the tachycardia was characterized by a marked decrease in left ventricular end-diastolic and stroke volumes, increased ejection rate and cardiac output, and no significant change in ejection fraction. The mechanism of the tachycardia was atrioventricular (A-V) reentrance using an anomalous pathway for retrograde conduction in seven patients, A-V nodal reentrance in five and atrial reentrance in one. Heart disease or very rapid heart rate during tachycardia modified the hemodynamic response and had a deleterious effect on ejection fraction. The hemodynamic features of paroxysmal supraventricular tachycardia are similar to those of rapid atrial pacing and not those of exercise.

562 Paroxysmal Atrial Fibrillation in the Wolff-Parkinson-White Syndrome

ROBERT A. BAUERNFEIND, CHRISTOPHER R. WYNDHAM, STEVEN P. SWIRYN, EDWIN V. PALILEO, BORIS STRASBERG, WILFRED LAM, DOUGLAS WESTVEER and KENNETH M. ROSEN

In this series of 88 patients with preexcitation the 30 patients with documented spontaneous atrial fibrillation were more likely to have inducible atrioventricular (A-V) reentrant tachycardia than were the patients without such documented atrial fibrillation. Organic heart disease of several different varieties was found in 13 (42 percent) of the patients with preexcitation and documented spontaneous paroxysmal atrial fibrillation. It is unclear why some patients with inducible reentrant tachycardia have atrial fibrillation and others do not. In the patients with organic heart disease atrial fibrillation could be related to hemodynamic changes. These results suggest that the administration of drugs to these patients to prevent paroxysmal supraventricular tachycardia could also prevent recurrence of atrial fibrillation since reentrant tachycardia may degenerate into rapid atrial fibrillation. The results imply that surgical division of the anomalous pathway (the retrograde limb of A-V reentrant tachycardia) could also prevent recurrence of atrial fibrillation.

570 Echocardiographic Abnormalities in Chronic Alcoholics With and Without Overt Congestive Heart Failure

EMMETT C. MATTHEWS, Jr., JULIUS M. GARDIN, WALTER L. HENRY, ALBERT A. Del NEGRO, ROSS D. FLETCHER, JERRY A. SNOW and STEPHEN E. EPSTEIN

M mode electrocardiographic studies in 11 symptomatic alcoholic patients with dilated (congestive) cardiomyopathy demonstrated significantly decreased left ventricular percent fractional shortening, along with significant increases in left ventricular systolic and diastolic dimensions, left atrial dimension and estimated left ventricular mass. In 15 (68 percent) of 22 asymptomatic chronic alcoholic patients similar studies showed significant increases in at least one of the following variables: left ventricular mass, left ventricular dimension, septal and left ventricular wall thicknesses and left atrial dimension; the most frequent abnormality (not considering thickness to radius ratio) was an increased left ventricular mass. These echocardiographic abnormalities in the group with asymptomatic chronic alcoholism did not correlate with the presence or absence of auscultatory abnormalities on physical examination and appear to reflect an earlier stage in the spectrum of alcoholic myocardial disease before the development of dilated congestive cardiomyopathy.

Continued on page A22

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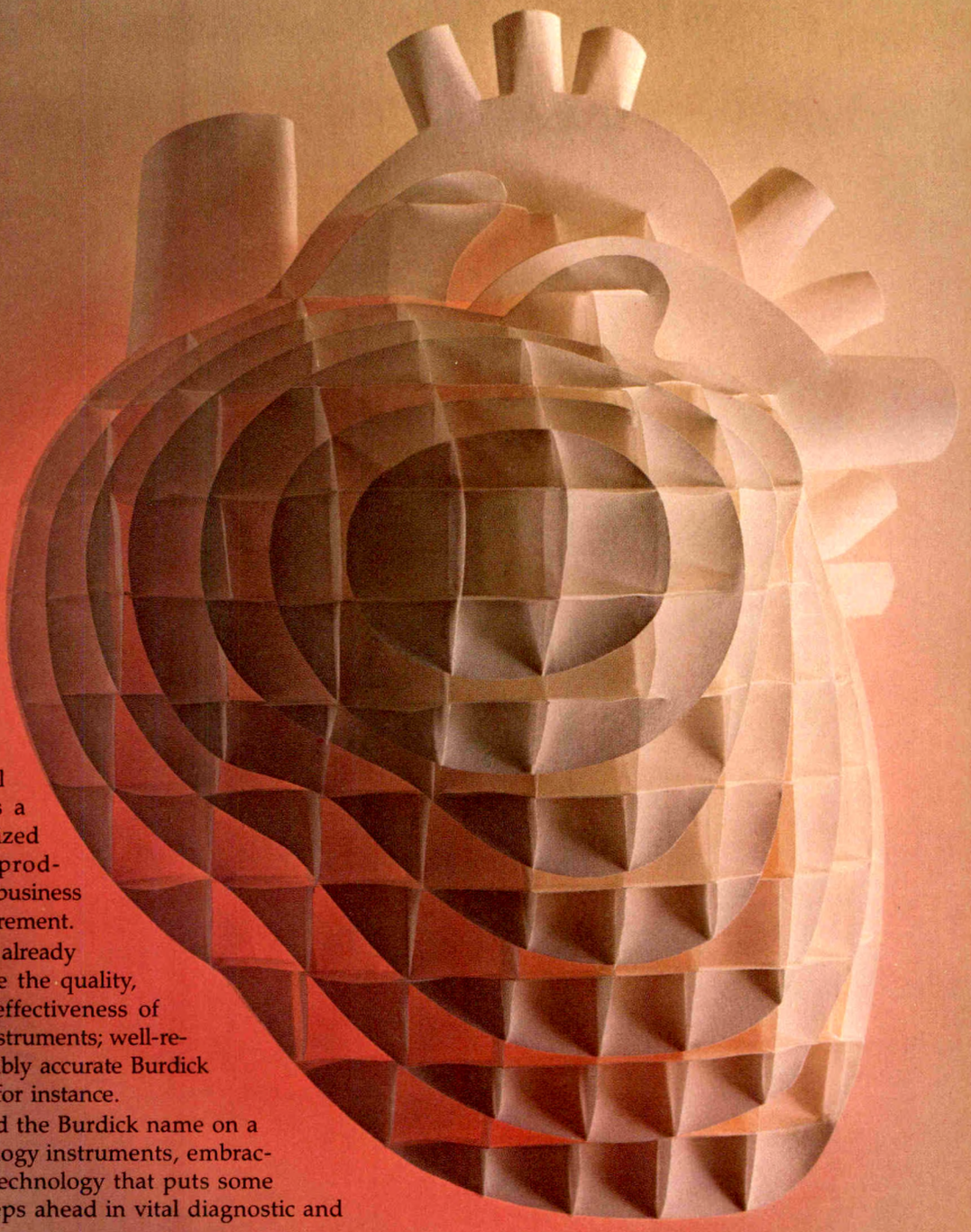

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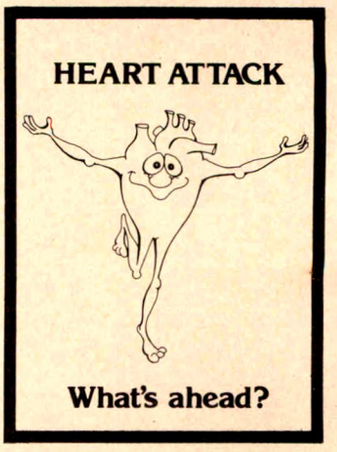
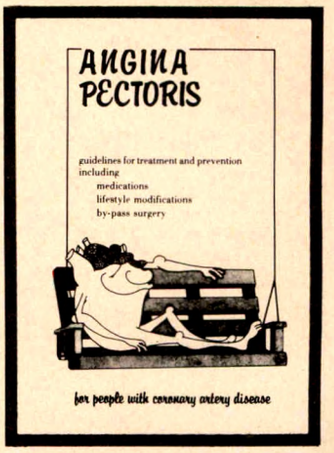
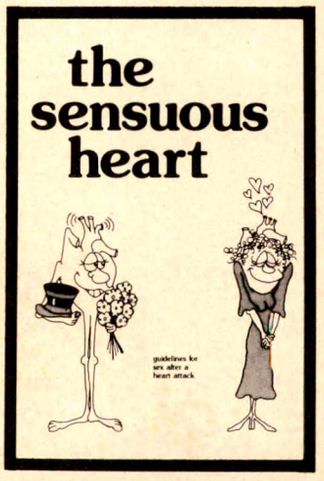


Explanations of coronary artery disease, angina pectoris, acute myocardial infarction or congestive heart failure can be very confusing to the average patient. This is why Pritchett & Hull patient education books are so important. The clear illustrations and concise texts help you explain complicated medical conditions. This leaves your patients feeling good about themselves and good about you. You can even personalize the material by using the ample space throughout each book to write in your special instructions about diet, medications or exercise, for example. Pritchett & Hull patient education books are for adult patients, and the reading level is that of an average, popular magazine. At present, these materials are used by hospitals, clinics and private practice physicians throughout the U.S. and in many foreign countries. Current titles include:





MOVING RIGHT ALONG AFTER OPEN HEART SURGERY
(Reviews by-pass surgery, valvular surgery, ASD repair) Also available in Spanish.

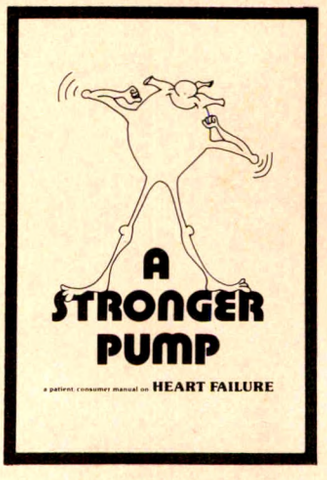
HEART ATTACK, WHAT'S AHEAD?
(Discusses AMI from hospitalization to recovery at home) Available in Spanish May 1, 1981.

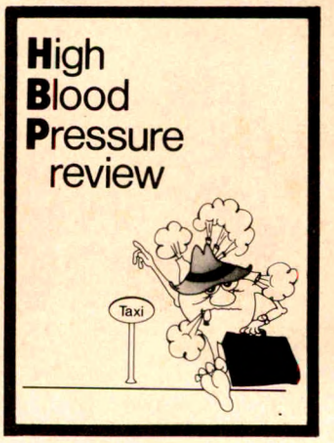
ANGINA PECTORIS
(Reviews risk factors for coronary artery disease, use of NTG; mentions potential for by-pass surgery)

THE SENSUOUS HEART
(Guidelines for sex after AMI)

A STRONGER PUMP
(Treatment for congestive heart failure explained in terms of rest, diet and medications)

HIGH BLOOD PRESSURE REVIEW
(For patients with essential hypertension. Includes information on diet, smoking, exercise and relaxation)





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Bayer® Aspirin

For reducing the risk of transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli

THE DAWN OF A NEW ERA IN PREVENTIVE MEDICINE

Recently, an official government bulletin indicated that the following professional guideline labeling will be published:

There is evidence that aspirin is safe and effective for reducing the risk of recurrent transient ischemic attacks or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli.

There is no evidence that aspirin is effective in reducing TIA's in women, or is of benefit in the treatment of completed strokes in men or women.

Patients presenting with signs and symptoms of TIA's should have a complete medical and neurologic evaluation.

Consideration should be given to other disorders which resemble TIA's.

It is important to evaluate and treat, if appropriate, other diseases associated with TIA's and stroke, such as hypertension and diabetes.

The recommended dosage for this new indication is 1,300 mg/day (650 mg twice/day or 325 mg four times a day).

Prostaglandin inhibition—the key to aspirin's success

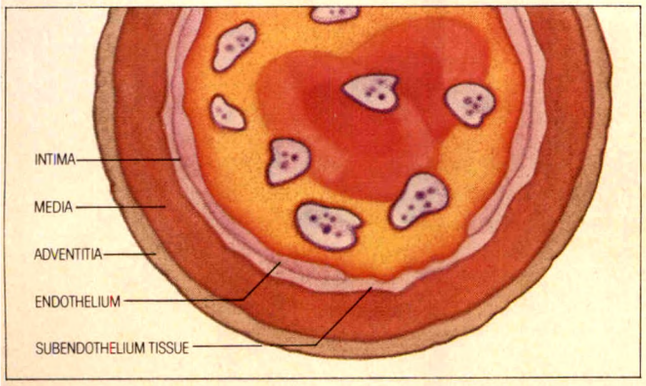
With the ability of aspirin to reduce the risk of recurrent TIA's and stroke clearly demonstrated in two major multicenter studies,[1,2] physicians throughout the country can now provide their own TIA patients with the prophylactic benefits of Bayer Aspirin.

At the same time, important new research is being conducted to determine the full scope of aspirin benefits in vascular disease...and in many other disorders involving prostaglandin synthesis.

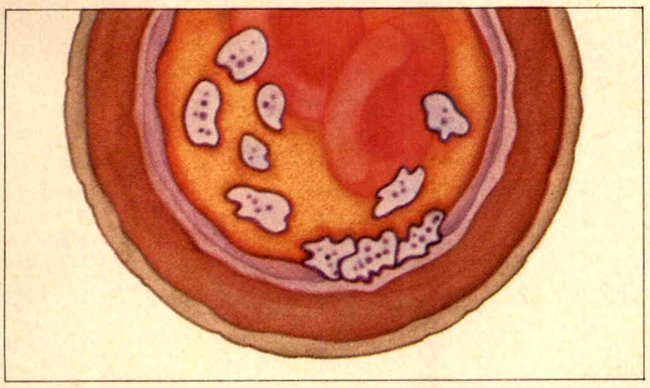
It has become apparent that many of aspirin's therapeutic effects—including its analgesic, antipyretic, anti-inflammatory and antithrombotic actions, can be traced entirely, or in part, to its ability to inhibit prostaglandin formation.

Prostaglandins are produced by every organ in the body with far reaching effects.[3] In vascular disease, for example, it is the excess production of the prostaglandin derivative, thromboxane A_2, that can ultimately lead to embolus formation.

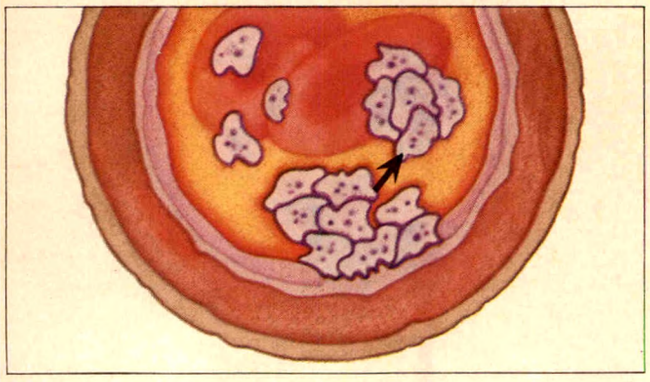
Cross-section of artery—artist's interpretation of circulating platelets encountering area of erosion in arterial wall.



Cerebrovascular clot formation begins when platelets circulating in the blood encounter an area of vascular erosion (usually predisposed by atherosclerosis)...with its exposed subendothelial tissue and collagen.



Through a series of prostaglandin interactions, a platelet collagen reaction takes place—first provoking platelet adhesion, then stimulating a self-perpetuating process of secretion, and finally, aggregation. Once formed, thrombi may dislodge.



By inhibiting platelet cyclo-oxygenase, an enzyme that mediates prostaglandin formation, aspirin inhibits thromboxane synthesis, prevents adhesion and thrombus formation and precludes thrombus dislodgment and subsequent TIA or stroke.

Bayer Aspirin and continuing investigations

Of the large number of pharmaceutical agents capable of altering platelet function, only aspirin has been shown to produce effects that are irreversible for the life of the platelet.[4]

Thus, the use of aspirin is being intensively investigated in a number of possible new clinical areas in which its antiplatelet, prostaglandin-inhibiting effects may be beneficial.

Not surprisingly, Bayer Aspirin has been the aspirin chosen for a large number of past and present studies. Bayer Aspirin actually exceeds U.S.P. requirements in critical areas such as aspirin content per tablet, dissolution time and free salicylic acid content. Over 100 quality-control tests help assure that the therapeutic dose recommended is the dose patients receive.

The Bayer Company is pleased not only to lend its continuing support to wide-ranging investigational studies, but to provide the medical community with comprehensive services and materials concerning aspirin.

The ability to reduce the risk of TIA or stroke with a drug as widely accepted, well tolerated and inexpensive as Bayer Aspirin, certainly represents the dawn of a new era in preventive medicine.

1. Fields, W.S. *et al.*: Stroke *8*:301 (May/June) 1977.
2. The Canadian Cooperative Study Group: N. Engl. J. Med. *229*:54 (July 13) 1978.
3. Robinson, D.W.: Resident & Staff Phys: *25*:92 (Feb) 1979.
4. Fields, W.S. Drugs *18*:150, 1979.

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EXPERIMENTAL STUDIES

579 Adrenergic Regulation of Total Systemic Distensibility. Venous Distensibility Effects of Norepinephrine and Isoproterenol Before and After Selective Adrenergic Blockade

DAVID L. RUTLEN, EDWARD W. SUPPLE and WILLIAM JOHN POWELL, Jr.

These experimental studies in 51 dogs before and after selective adrenergic receptor blockade with phenoxybenzamine and propranolol revealed that the norepinephrine effect was mediated almost entirely through alpha adrenergic receptor stimulation and the isoproterenol effect mostly through beta adrenergic stimulation. Alpha and beta adrenergic receptor stimulation with norepinephrine and isoproterenol is associated with sustained increases in total systemic vascular distensibility and would be expected to be associated with diminished increases in venous pressure, venous return and cardiac performance when a given amount of volume is added to the intravascular space. These data suggest that the increase of sympathetic tone in the patient with congestive heart failure may benefit the patient in that the venous pressure would be increased much less for a given increment in vascular volume and thereby protect the patient from central volume overload, pulmonary edema or ascites.

589 Production of a Critical Coronary Arterial Stenosis in Closed Chest Laboratory Animals. Description of a New Nonsurgical Method Based on Standard Cardiac Catheterization Techniques

HENRY GEWIRTZ and ALBERT S. MOST

This study demonstrates that a critical intraluminal coronary arterial stenosis can be created rapidly and maintained in a closed chest dog by inserting an occlusive plastic truncated cone with a narrow central internal lumen into the animal's left anterior descending coronary artery using standard cardiac catheterization technique. During atrial pacing the endocardial to epicardial flow ratio decreased considerably in myocardium distal to the stenosis but remained unchanged in the left circumflex arterial zone. The data further indicate that the subendocardial layer of the heart is most vulnerable to ischemia and that some vasodilator reserve persists in epicardial vessels distal to a critical coronary stenosis. This method avoids many problems associated with open heart surgery and general anesthesia and provides an improved model for the study of myocardial blood flow and left ventricular function.

597 Differential Effects of Renografin-76 on the Ischemic and Nonischemic Myocardium

HAJIME YAMAZAKI, VIDYA S. BANKA, MONTY M. BODENHEIMER, SHIGEHITO HATTORI, JAI B. AGARWAL and RICHARD H. HELFANT

This dog study demonstrates that the myocardial depressant effects of an intracoronary injection of Renografin-76 are more pronounced and 4 to 5 times more prolonged in the ischemic myocardium than in normally perfused myocardium. These effects are neither abolished by the prior administration of nitroglycerin nor solely due to the hyperosmolarity or sodium concentration of the solution. Coronary flow reserve appears to play an important role in determining the duration of the depressant effects produced by injection of contrast medium. These results may be particularly relevant to coronary injections of Renografin-76 in patients with left main coronary arterial stenosis in whom the risk of coronary arteriography is recognizably high.

METHODS

603 Accuracy of Systolic Time Intervals in Detecting Abnormal Left Ventricular Performance in Coronary Artery Disease

RICHARD S. STACK, YOUNG H. SOHN and ARNOLD M. WEISSLER

This prospective analysis of noninvasively determined systolic time intervals as a measure of global left ventricular performance in 66 consecutive patients with a previous myocardial infarction, 44 patients with angina pectoris and no evidence of a previous myocardial infarction and 41 control patients with atypical chest pain and normal coronary arteries and left ventricular performance showed a correlation of 0.84 for the ratio of preejection period and left ventricular ejection time (PEP/LVET). Among the patients with coronary artery disease with and without previous myocardial infarction, PEP/LVET proved equivalent to the ejection fraction in identifying the patients with normal and abnormal left ventricular performance. On the basis of the group data analysis, the investigators conclude that PEP/LVET affords an accurate expression of the global performance of the left ventricle in coronary artery disease.

Continued on page A28

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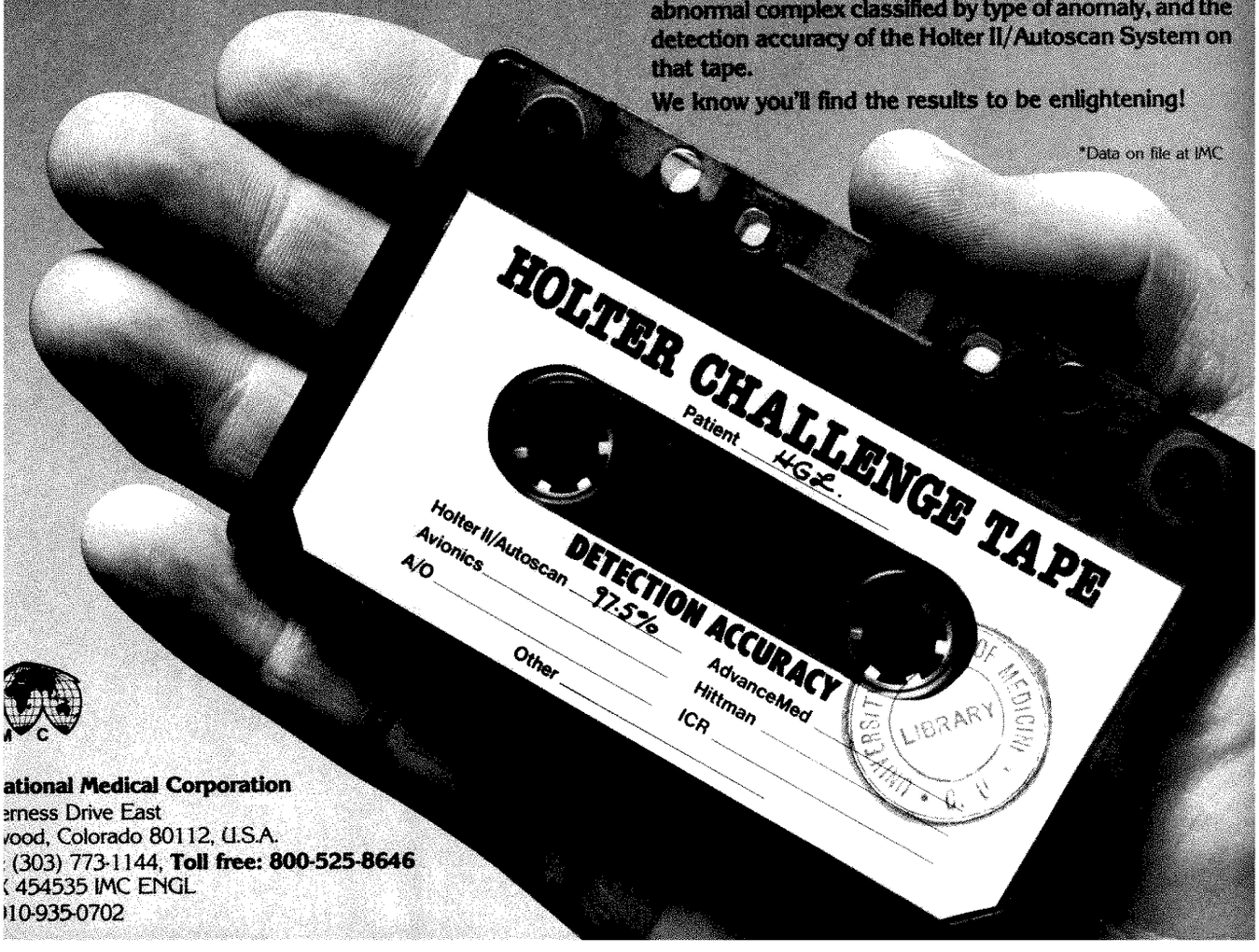
We know you'll find the results to be enlightening!

*Data on file at IMC



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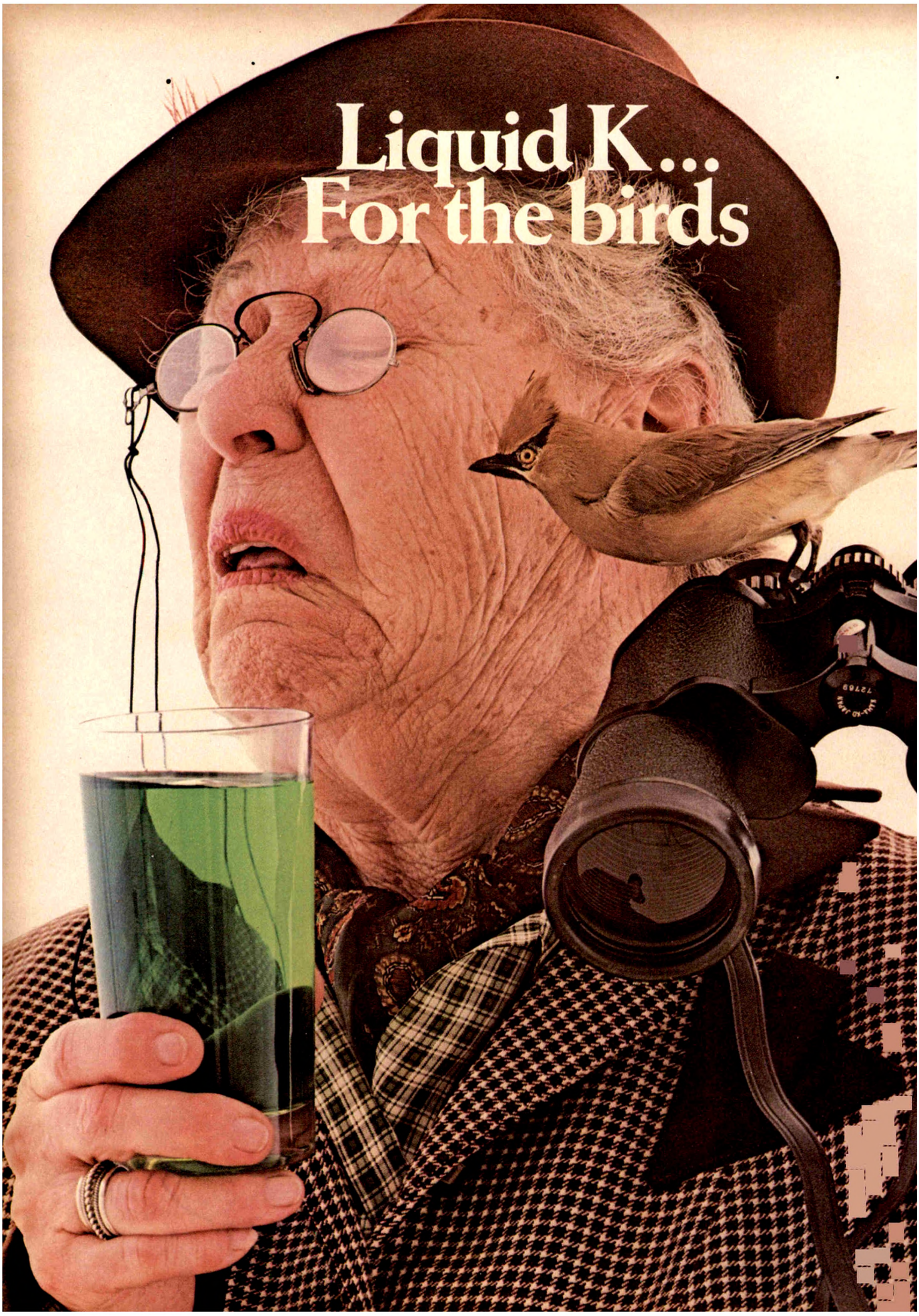
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There are 5 years of U.S. clinical experience behind Slow-K. The 8 mEq tablet has proved safe and effective in over 4 million patients in the U.S. alone.*,†

25¢ a day

The cost of a day's therapy averages less than a quarter.‡

Acceptability

Slow-K has an unparalleled record of patient compliance.

No taste problems

Patients prefer Slow-K to unpalatable liquid.

Salt of choice (KCl)

The preferred salt to correct the hypokalemic alkalosis that may result after long-term use of diuretics.

*Slow-release potassium chloride tablets should be reserved for patients who cannot tolerate or have compliance problems with liquid K preparations. The total number of GI lesions in both foreign countries and the United States remains less than one per 100,000 patient-years.

†Data on file, CIBA Pharmaceutical Company.

‡Average cost per day based on Pharmaceutical Data Services audit.

4 million patients,
5 years of U.S. clinical experience†

Slow-K®

CIBA 165

potassium chloride slow-release tablets 8 mEq

Please turn page for brief prescribing information.

CIBA

SLOW-K®
potassium chloride slow-release tablets

DESCRIPTION
Slow-K is a sugar-coated (not enteric-coated) tablet containing 600 mg potassium chloride (equivalent to 8 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS
BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.

3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS
In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg*, spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS
Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium-Sparing Diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg*, spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Slow-K is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. Slow-K should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS
Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion, particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram, and clinical status of patient.

ADVERSE REACTIONS
Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE AND ADMINISTRATION
Usual dietary intake of potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: Slow-K slow-release tablets must be swallowed whole and never crushed or chewed.

C78-23 (4/78)

Consult complete product literature before prescribing. 128-6089-A

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Division of CIBA-GEIGY Corporation
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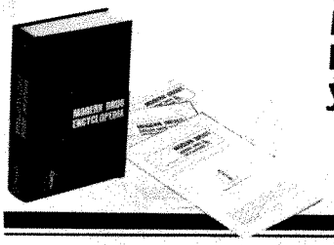
C I B A

How thorough and unbiased is your drug reference?



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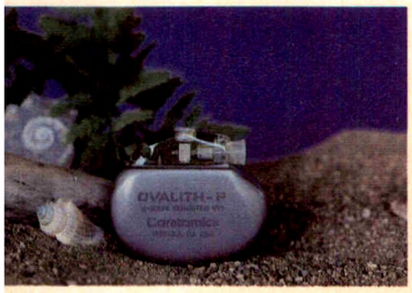

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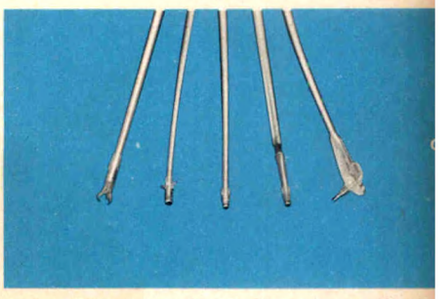

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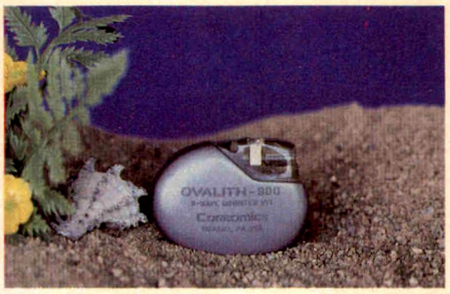

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Lithium Powered Pacemaker

OVALITH-BP Bipolar
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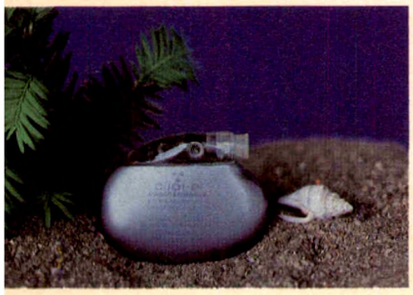

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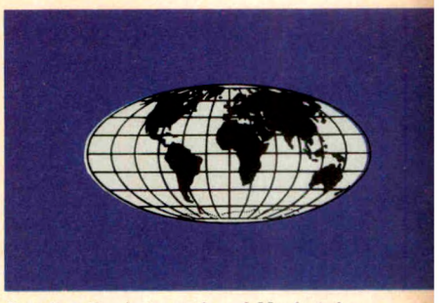
C-101 Unipolar
Isotopic Powered Pacemaker



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610 **Noninvasive Detection of Left Ventricular Dysfunction With A Portable E Scintillation Probe Device**

ARNOLD STRASHUN, STEVEN F. HOROWITZ, STANLEY J. GOLDSMIT ADAM DICKER, KENNETH MICELI and RICHARD GORLIN

This study of left ventricular function data in 68 patients suggests that radior cardiographic-gated scintillation probe is a sensitive, rapid and less costly p diac dysfunction with a yield similar to that of the more costly gamma camer fraction correlation was better in patients with uniform wall motion than in t variables with this technique provided 100 percent sensitivity, specificity a normal left ventricular performance. Probe-monitored stress tests may pr nique than the resting procedure described in this study.

618 **Method for Quantitative Analysis of Regional Left Ventricular Function V Blood Pool Scintigraphy**

SILVIO E. PAPAPIETRO, MICHAEL V. YESTER, JOSEPH R. LOGIC, W. JOHN A. MANTLE, WILLIAM J. ROGERS, RICHARD O. RUSSELL, Jr. a

This study of 33 patients undergoing biplane left ventricular cineangiograp of segmental scintigraphic ejection fraction obtained from first pass and mult scintigrams performed in the right anterior oblique and axial left anterior obli evaluation of the function of various segments of the left ventricular regions v interobserver variability. Segmental scintigraphic ejection fraction can easil giocardiograms and may prove useful in quantitating infarct size, monitoring and evaluating changes resulting from physiologic, metabolic and surgical ir

626 **Intravenous Xenon-133 for the Determination of Radionuclide First Pass Fraction**

MARK J. GOLDBERG, JOSEPH MANTEL, MARK FRIEDIN, ROBERT RUS

First pass determinations of right ventricular ejection fraction with both xer subjects showed excellent correlation between the two methods. The rapid p from the body allows multiple first pass right ventricular ejection fraction d of time without significant radiation exposure for the patient. The main disad its cost. The rapid pulmonary elimination of xenon-133 precludes determina fraction from the same first pass bolus injection except in patients with a rig

PEDIATRIC CARDIOLOGY

631 **Hereditary Dysplasia of the Pulmonary Valve in Beagle Dogs. Pathologi**

DONALD F. PATTERSON, MARK E. HASKINS and WILLIAM R. SCHNA

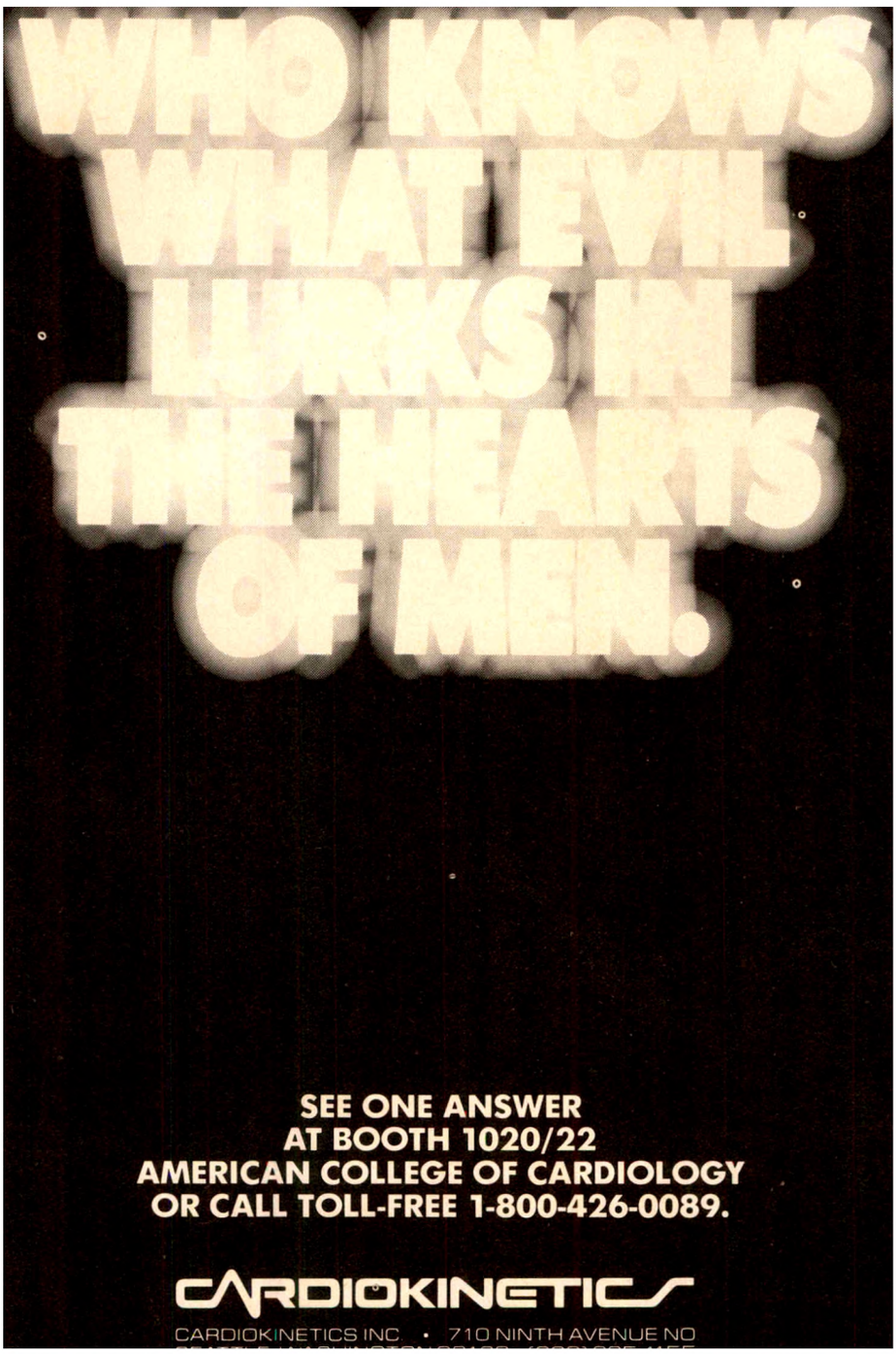
Hereditary pulmonary valve dysplasia is the term proposed by the investigat trum of pulmonary valve abnormalities found in a specially bred colony of be Genetic studies indicated that pulmonary valve dysplasia is not inherited as breeding increases the risk of developing it. The underlying developmental nary valve anlagen, leads to a wide range of pulmonary valve anomalies bu tions of the heart or other body systems. The genetic data in beagles are con cerning the genetic factors of isolated pulmonary stenosis in human beings. I is involved and inbreeding increases the risk of this anomaly in affected offs

642 **Management of Symptomatic Infants With Anomalous Origin Of the Left Pulmonary Artery**

DAVID J. DRISCOLL, MICHAEL R. NIHILL, CHARLES E. MULLINS, DEN DAN G. McNAMARA

Anomalous origin of the left coronary artery from the pulmonary artery occu stitutes 0.24 percent of all congenital anomalies. The results of surgical and congestive heart failure due to this anomaly during the first 6 months of life ar ing the 1st year of life was disappointing since only two of the eight surgical

Continued on page A33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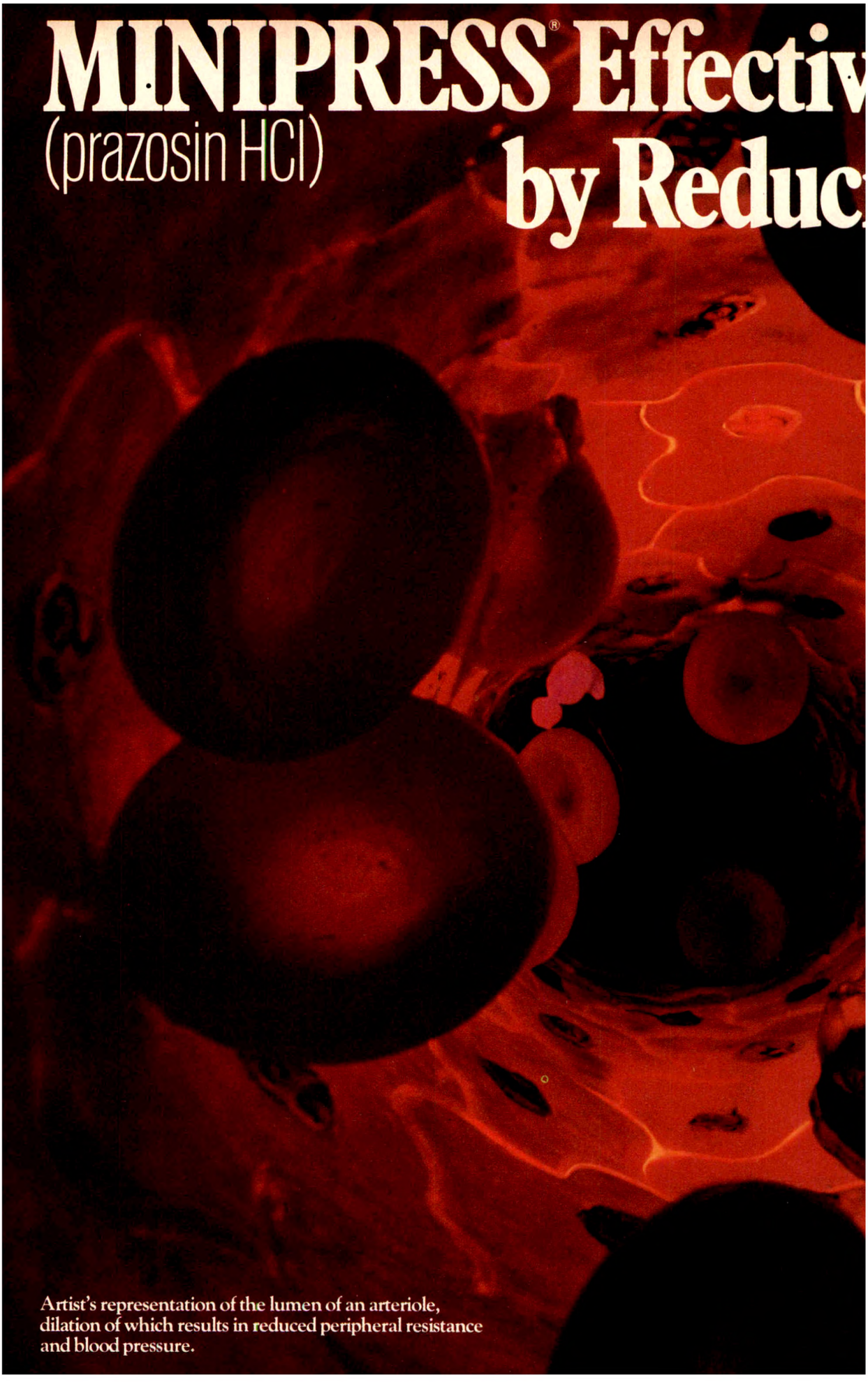
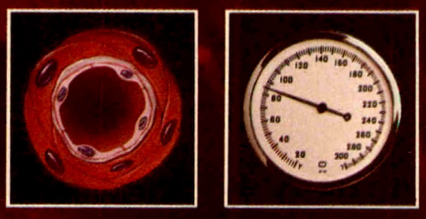


Artist's representation of the lumen of an arteriole, dilation of which results in reduced peripheral resistance and blood pressure.

Controls Hypertension Peripheral Resistance



- MINIPRESS Reduces Mean Arterial Pressure
- MINIPRESS Reduces Total Peripheral Resistance
- MINIPRESS Does Not Reduce Cardiac Index

...and Maintains These Effects Over the Long Term

Relative hemodynamic changes at rest and during exercise after one year of prazosin therapy in 10 hypertensive patients. Adapted from Lund-Johansen[1]

Rest Exercise

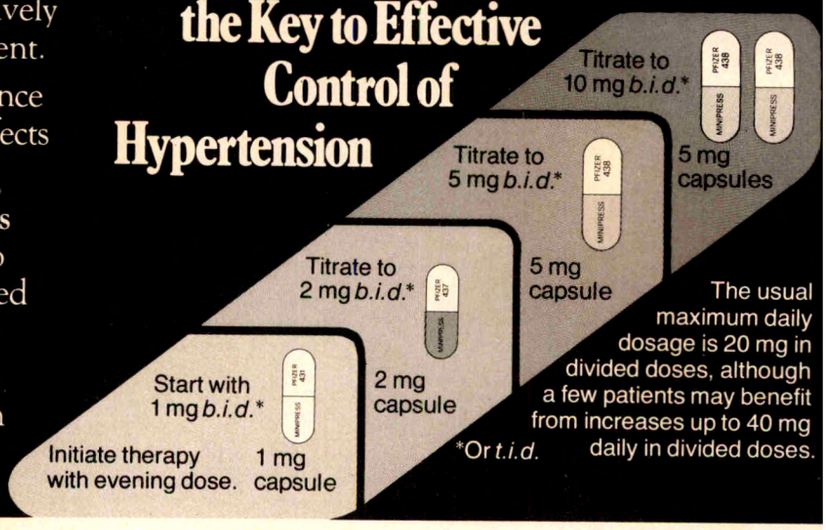
MINIPRESS®

(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

MINIPRESS®
(prazosin HCl) Capsules 1 mg, 2 mg, 5 mg

- **Effectively lowers elevated blood pressure by reducing peripheral resistance.**
- **Maintains cardiac output** which allows patients to maintain an active life style.
- **Maintains renal blood flow and glomerular filtration rate** so it can be used effectively even in patients with renal impairment.
- **Not a CNS agent** so patients experience few of the troublesome CNS side effects that impair their quality of life.
- **Cardiovascular response to exercise is preserved** so patients are less likely to experience the fatigue often associated with beta-blocker therapy.
- **A small percentage of patients** have experienced orthostatic hypotension and syncope.

B.I.D. Dosage Titration... the Key to Effective Control of Hypertension



The usual maximum daily dosage is 20 mg in divided doses, although a few patients may benefit from increases up to 40 mg daily in divided doses.

BRIEF SUMMARY
MINIPRESS® (prazosin hydrochloride) CAPSULES *For Oral Use*

INDICATIONS: MINIPRESS® (prazosin hydrochloride) is indicated in the treatment of hypertension. As an antihypertensive drug, it is mild to moderate in activity. It can be used as the initial agent or it may be employed in a general treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

WARNINGS: MINIPRESS (prazosin hydrochloride) may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of MINIPRESS (prazosin hydrochloride). The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of MINIPRESS (prazosin hydrochloride). The 2 and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of MINIPRESS (prazosin hydrochloride) therapy.

Usage in Pregnancy: Although no teratogenic effects were seen in animal testing, the safety of MINIPRESS (prazosin hydrochloride) in pregnancy has not been established. MINIPRESS (prazosin hydrochloride) is not recommended in pregnant women unless the potential benefit outweighs potential risk to mother and fetus.

Usage in Children: No clinical experience is available with the use of MINIPRESS (prazosin hydrochloride) in children.

ADVERSE REACTIONS: The most common reactions associated with MINIPRESS (prazosin hydrochloride) therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

The following reactions have been associated with MINIPRESS (prazosin hydrochloride), some of them rarely. (In some instances exact causal relationships have not been established).

Gastrointestinal: vomiting, diarrhea, constipation, abdominal discomfort and/or pain.

Cardiovascular: edema, dyspnea, syncope, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia.

Dermatologic: rash, pruritus.

Genitourinary: urinary frequency, incontinence, impotence.

EENT: blurred vision, reddened sclera, epistaxis, tinnitus, dry mouth, nasal congestion.

Other: diaphoresis.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

DOSAGE AND ADMINISTRATION: The dose of MINIPRESS (prazosin hydrochloride) should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose: 1 mg two or three times a day. (See Warnings).

Maintenance Dose: Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs: When adding a diuretic or other antihypertensive agent, the dose of MINIPRESS (prazosin hydrochloride) should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

HOW SUPPLIED: MINIPRESS (prazosin hydrochloride) is available in 1 mg (white #431), 2 mg (pink and white #437) capsules in bottles of 250, 1000, and unit dose institutional packages of 100 (10 x 10's); and 5 mg (blue and white #438) capsules in bottles of 250, 500 and unit dose institutional packages of 100 (10 x 10's).

More detailed information available on request.

Reference:

1. Lund-Johansen P: Hemodynamic changes at rest and during exercise in long-term prazosin therapy for essential hypertension, in *Prazosin Clinical Symposium Proceedings*, published as a special report by *Postgrad Med.* New York, McGraw-Hill Book & Education Services Group, 1975, pp 45-52.

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contrast, in the 15 patients who received medical treatment, operation was delayed until a mean age of 7.5 years, and 13 of the 15 survived until a mean age of 14.5 years. Delay of operative intervention until at least age 18 months is therefore recommended because coronary arterial surgery in the 1st year of life in infants with severely depressed myocardial function has an extremely high mortality rate of 75 percent and because many sick infants can be treated medically and survive.

649 **Coronary Artery Disease in the Hurler Syndrome**

FRANK C. BROSIUS, III and WILLIAM C. ROBERTS

Necropsy data in six patients aged 3 to 16 years with the Hurler syndrome revealed narrowing of the major epicardial coronary arteries, produced mainly by a combination of Hurler cells, granular cells, collagen and acid mucopolysaccharide material. The coronary disease is usually diffuse and severe. In fact, the Hurler syndrome is responsible for the most severe coronary narrowing in childhood. The lumen in every 5 mm segment of coronary artery was centrally located, or nearly so, and all portions of the arterial lining were covered by the Hurler type plaque. Despite these severe lesions, no patient had clinical symptoms of cardiac dysfunction or evidence of myocardial ischemia during life.

654 **Two Dimensional Echocardiographic Evaluation of Mustard Operation for d-Transposition of the Great Arteries**

KALIM U. AZIZ, MILTON H. PAUL, SAROJA BHARATI, ROGER B. COLE, ALEXANDER J. MUSTER, MAURICE LEV and FAROUK S. IDRISS

This study demonstrates the value of two dimensional sector scan echocardiography in assessing qualitatively and quantitatively the morphologic structural abnormalities of the surgically revised systemic and pulmonary venous atria in 17 patients with d-transposition of the great arteries after the Mustard operation. The site and severity of these abnormalities in 10 of the patients correlated accurately with the angiographic appearances. Tricuspid regurgitation in six patients was shown to lead to a grossly enlarged pulmonary venous atrium with dilatation in all of its segments. The echocardiographic diagnosis of tricuspid regurgitation is indirect because regurgitation of the blood into the pulmonary venous atrium cannot be observed directly. The cause of the tricuspid insufficiency in complete d-transposition is probably related to pre-, intra- and postoperative factors. This noninvasive method can facilitate longitudinal follow-up and permit assessment of progression of the lesions during growth.

REPORTS ON THERAPY

665 **Comparison of Hemodynamic Actions of Pirbuterol and Dobutamine on Cardiac Function in Severe Congestive Heart Failure**

NAJAM A. AWAN, KATHLEEN E. NEEDHAM, MARK K. EVENSON and DEAN T. MASON

Comparison of the hemodynamic effects of pirbuterol, a new oral beta adrenergic receptor agonist, with those of intravenous dobutamine in nine patients with severe heart failure demonstrates oral pirbuterol exerts dobutamine-like beneficial hemodynamic effects on left ventricular pump function but causes a greater decrease in total systemic vascular resistance consistent with its combined inotropic and peripheral vasodilator actions. Neither drug caused left ventricular ischemia or increased ventricular arrhythmia. The beneficial effects of pirbuterol are probably caused by its combined central inotropic and peripheral vasodilator actions. These results indicate that oral pirbuterol should be included in the pharmacologic treatment of severe chronic congestive heart failure and may represent a significant therapeutic advance.

670 **Hemodynamic Effects of Intravenous Prenalterol in Severe Heart Failure**

PHILIP C. KIRLIN and BERTRAM PITT

The administration of intravenous prenalterol (a new catecholamine-like inotropic agent) to nine patients with chronic severe low output heart failure significantly improved their hemodynamic state as measured by increased left ventricular ejection fraction (to 26 ± 4 percent), decreased left ventricular filling pressure (to 21 ± 8 mm Hg), increased cardiac index (to 2.4 ± 0.6 liters/min per m^2) and increased left ventricular stroke work index (to 26 ± 8 g-m/m^2). The decrease in the abnormally elevated pulmonary vascular resistance after administration of this drug was comparable with similar changes noted with dobutamine. Significant adverse effects included increased ventricular ectopic beats in two patients and asymptomatic ventricular tachycardia in two patients. The combination of severe ischemic heart failure and previous digoxin therapy warrants particular caution in the administration of prenalterol.

Continued on page A36

FREEZE
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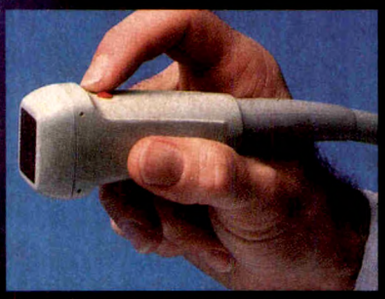
THE IMAGE QUALITY IS EVERYTHING YOU'D EXPECT FROM HEWLETT-PACKARD.

Compact, cart-mounted mobile system is ideal for the cardiology lab as well as coronary care units.

Now you can get a full-featured, real time, phased array, two-dimensional scanner that offers meaningful technological advances in almost every area.

It's the real time scanner for echocardiography from Hewlett-Packard. Incorporating a small 64-element array transducer, innovations in signal processing, microcomputer-based circuitry and a new digital scan converter, the HP system not only provides superior image quality, it does it at a price

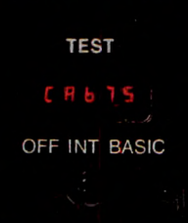


Small, lightweight, handheld transducer minitaped and replayed on standard video equipment.

that compares favorably to conventional mechanical scanners.

Superb resolution for accurate diagnosis.

The HP Ultrasound Imaging System provides extraordinarily high resolution images at all depths throughout the field of view. Its wide aperture, small electronic array transducer and automatic focusing technique give you extremely accurate images—even in areas near the transducer and deep in the body. And since the entire field of view is in focus at all times, you can see shallow as well as deep structures in the same picture. The compact, lightweight transducer fits in intercostal spaces and enhances the scanning of the heart.



Built-in self-test capability assures the operator that everything is functioning properly.

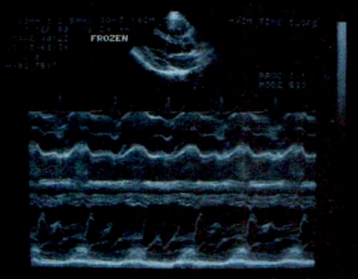
A new method of digital scan conversion eliminates radial scan lines, moiré patterns and blocky digital artifacts, and results in an accurate image. A total of 30 shades of gray can be processed, so small variations in tissue density can be distinguished.

Quantitative analysis on both the M-mode and two-dimensional image is accomplished by an electronic cursor.

The wide dynamic range of the system's circuitry produces a sharp image, while reducing background noise and clutter. The system's high-resolution, high-speed (twice the conventional TV rate) display gives you an easy-to-see

Simple, centralized controls for easy operation.

With the HP scanner, you not only get superior image quality, you get it quickly and easily. All major controls are logically located in one central area. You can scan patient after patient with a minimum of control adjustments. The HP scanner even provides a built-in self-test capability, so you know that everything is functioning properly.



M-mode is easily visualized on the same screen as the two-dimensional sector.

All this and more, for less.

While the HP scanner delivers exceptional image quality and easy operation, it doesn't compromise features. It offers quantitative analysis capabilities, ECG triggering, and "freeze-frame." You can view the sector scan and the M-mode display on the same screen simultaneously. In addition, the dual M-mode display lets you analyze two areas of the heart at the same time.

For more information on this full-featured, surprisingly affordable HP Model 77020A Ultrasound Imaging System for echocardiography, call your local Hewlett-Packard sales office, or write: Wayne Wager, Hewlett-Packard, 175 Wyman

676 **Ventricular Tachycardia: Prediction of Response to Oral Aprindine With Intravenous Aprindine**

BORIS STRASBERG, EDWIN PALILEO, DARREL PRECHEL, ROBERT BAUERNFEIND, STEVEN SWIRYN, CHRISTOPHER R. WYNDHAM, RAMESH C. DHINGRA, RICHARD KEHOE and KENNETH M. ROSEN

The intravenous administration of aprindine to 25 patients with ventricular tachycardia refractory to conventional antiarrhythmic agents helped to predict the subsequent response to oral aprindine. Eleven patients (43 percent) had conversion to sinus rhythm with intravenous aprindine and remained free of ventricular tachycardia during oral treatment with aprindine for a follow-up period of 2 to 38 months. It is unclear why patients with incessant ventricular tachycardia tended to respond whereas those with paroxysmal sustained ventricular tachycardia did not. Twelve patients manifested mild neurotoxicity, consisting primarily of mild tremor or mild ataxia, or both, after the oral dose of aprindine was established.

SEMINAR:

CARDIOVASCULAR FUNCTION IN RESPIRATORY FAILURE—I

Richard A. Matthay, MD and Lawrence D. H. Wood, MD, Guest Editors

683 **Introduction: The Functionally Integrated Cardiovascular-Pulmonary Unit**

RICHARD A. MATTHAY and LAWRENCE D. H. WOOD

686 **Contractile Mechanisms and Interaction of the Right and Left Ventricles**

KARL T. WEBER, JOSEPH S. JANICKI, SANJEEV SHROFF and ALFRED P. FISHMAN

This review of the physiologic behavior of the cardiopulmonary unit provides insight into the clinical recognition and management of the patient with respiratory failure. The cardiopulmonary unit consists of the right and left ventricles (two in-series pumps composed of cardiac muscle), which are mechanically coupled by the lungs. The factors controlling cardiac muscle shortening also regulate the pumping behavior of the ventricles. The interventricular septum, pericardium and intrathoracic pressure also influence the behavior of this system.

696 **Control of Cardiac Output by Systemic Vessels. Circulatory Adjustments to Acute and Chronic Respiratory Failure and the Effect of Therapeutic Interventions**

HOWARD S. GOLDBERG and JOHN RABSON

This review presents an integrated approach to circulatory function and its adjustments in patients with acute and chronic respiratory failure based on the following factors that influence venous return: (1) mean pressure in the systemic vasculature, (2) right atrial pressure, and (3) the resistance to venous return. Right atrial pressure depends on the contractile state of the right and left ventricles, the load on them, the presence or absence of pericardial effusion and alterations in pleural pressure with positive pressure ventilation. Diuretic drugs, cardiac glycosides, other inotropic or vasoactive drugs and positive pressure ventilation may affect the circulation by influencing the relation between the mean systemic pressure and right atrial pressure. For reasons presented in this review, cardiac glycosides may not be of value and the overly vigorous use of diuretic agents may even be potentially dangerous in the management of patients with cor pulmonale.

DIAGNOSTIC SHELF

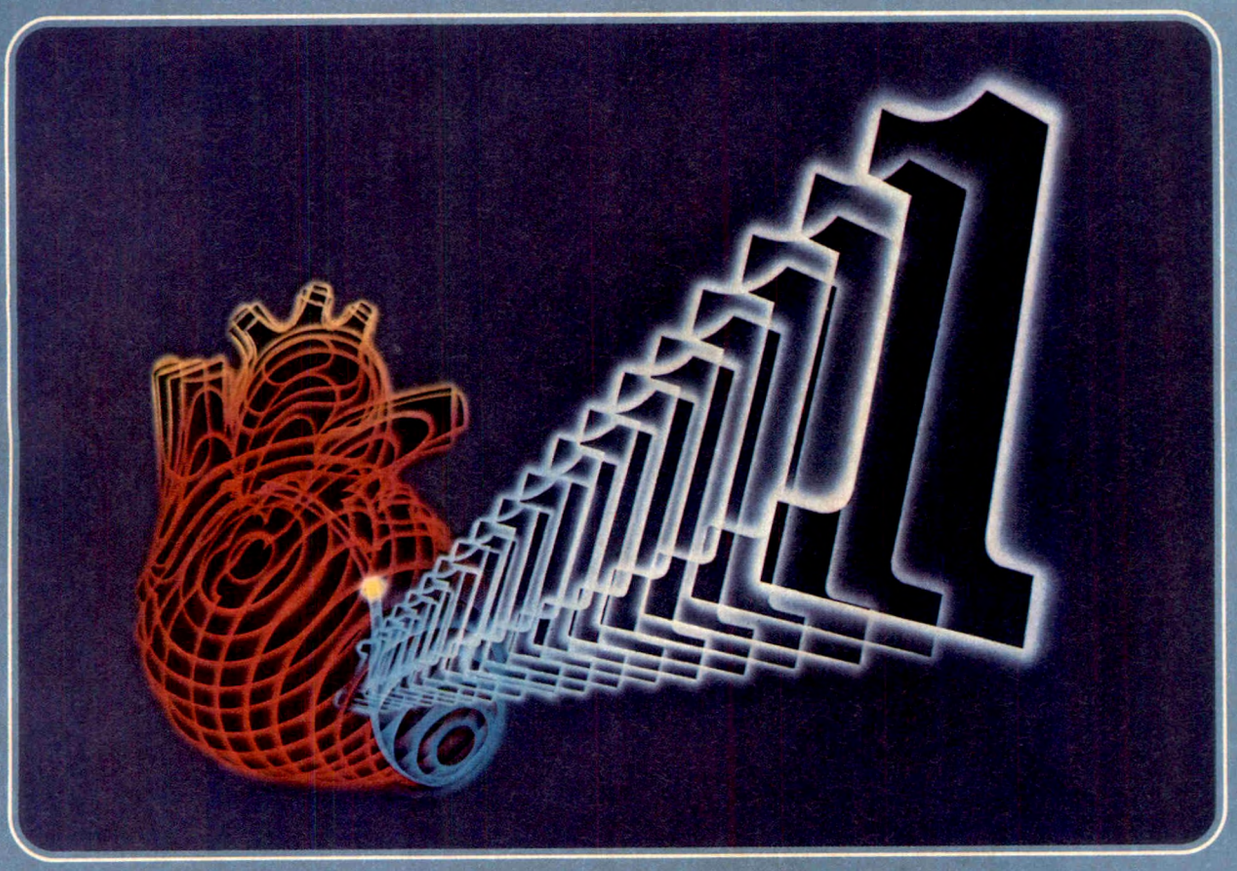
703 **Observations on Spontaneous Termination of Atrioventricular Nodal Reentrant Tachycardia**

PEDRO BRUGADA, DAVID ROSS, FRITS W. H. M. BÄR, EDDY J. VANAGT, WILLEM R. M. DASSEN and HEIN J. J. WELLENS

These observations on the spontaneous termination of tachycardia during programmed electrical stimulation of the heart in two patients with atrioventricular nodal tachycardia emphasize how conduction over a third pathway connected to the reentry circuit can produce refractoriness in the reentry circuit and terminate the arrhythmia. This pathway was located extranodally in one patient and intranodally in the other. Present methods of investigation in the intact human heart are not yet refined enough to uncover most of these complex mechanisms.

Continued on page A42

CORGARD®
nadolol tablets



The first and only beta-blocker with once-a-day dosage

In the treatment of angina pectoris

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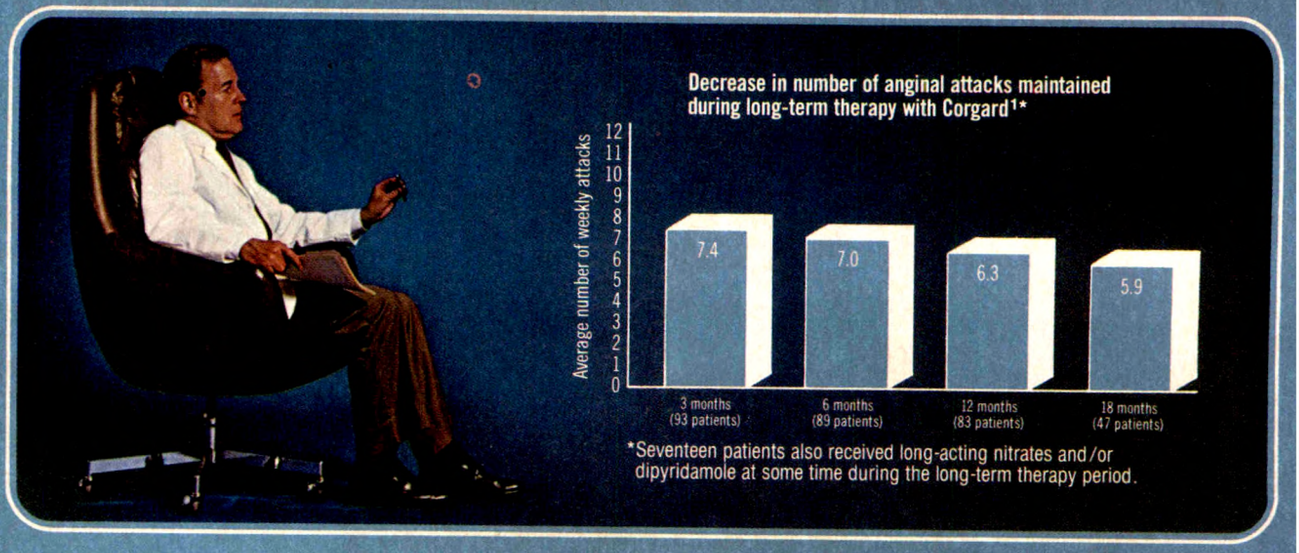
See last page of this advertisement for brief summary.



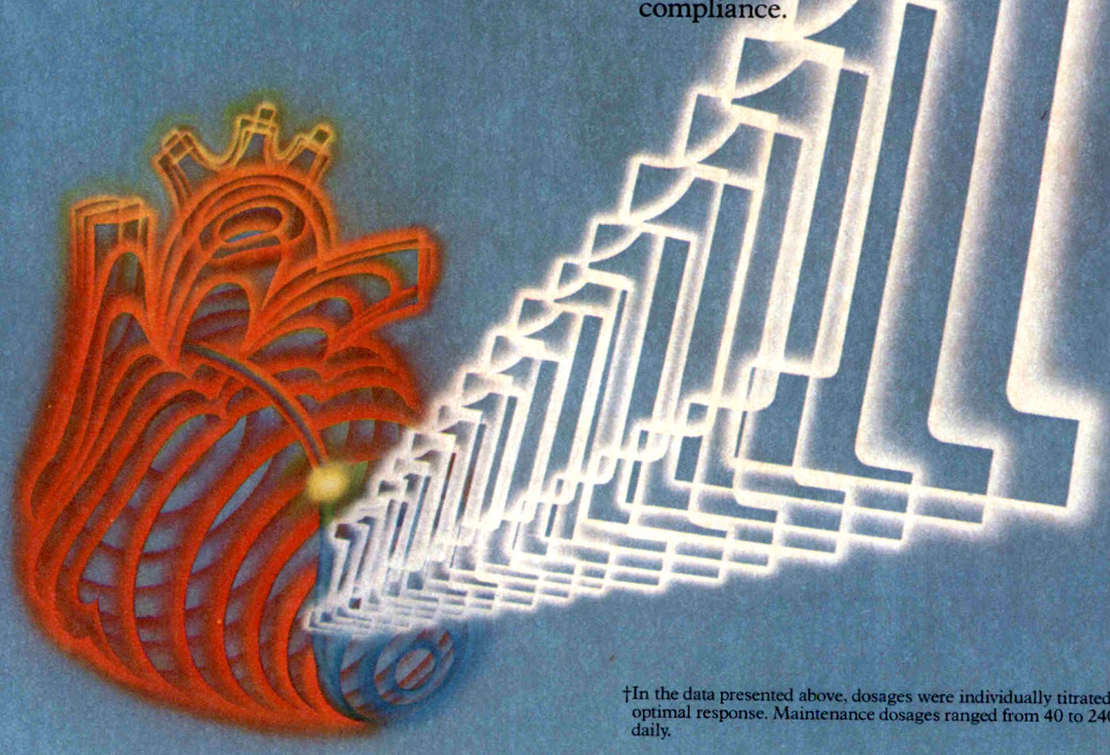
CORGARD® [nadolol tablets]:

Once-a-day, everyday, Corgard offers round-the-clock protection

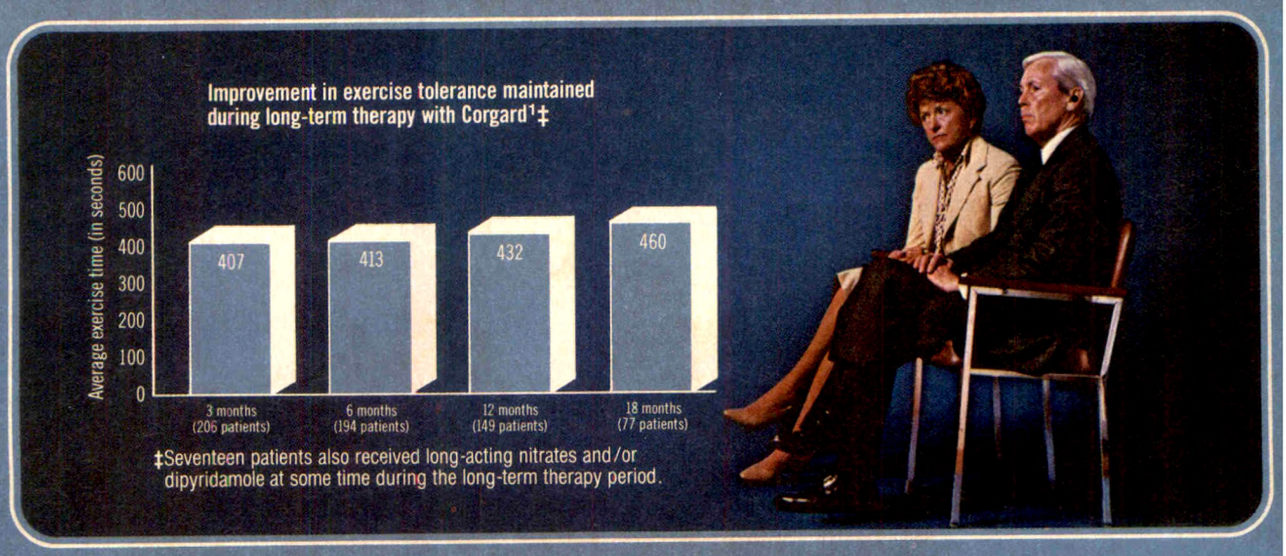
A single daily dose of Corgard offers prophylaxis in angina pectoris, helping to protect the patient all day and all night from painful attacks. And in extended clinical studies, the efficacy of Corgard — as demonstrated by a decreased rate of anginal attacks and an increase in exercise tolerance — was maintained.[1]

Once-a-day, everyday, Corgard decreases the frequency of anginal attacks

Corgard taken just once daily offers round-the-clock protection from angina pain. In one short-term study, Corgard, once a day, decreased the average number of anginal attacks per week in 115 patients with angina, from 13.6 pretherapy to 6.4 at the end of 14 weeks of therapy, a mean decrease of 59%.[1†] In 19% of the 115 patients, anginal attacks were completely eliminated. And the long half-life (20 to 24 hours) makes Corgard the once-a-day beta-blocker, promoting patient compliance.



†In the data presented above, dosages were individually titrated to achieve optimal response. Maintenance dosages ranged from 40 to 240 mg Corgard daily.



Effective control of angina pectoris

Once-a-day, everyday, Corgard increases exercise tolerance

Corgard allows the angina patient to do more. In 147 patients in the same short-term study as the one at left, Corgard, once a day, increased ergometry time by 25%, improving exercise tolerance from an average of 365 seconds pretherapy to 427 seconds at the end of 14 weeks of therapy.[1] In 21% of the 147 patients, the end point of exercise was fatigue rather than angina pain. And the single daily dose of Corgard can be taken at the patient's convenience, without regard to meals.

Once-a-day, everyday, Corgard decreases nitroglycerin usage[1]

Corgard blocks catecholamine influence on myocardial activity, decreases myocardial oxygen demand, and does not have a direct myocardial depressant effect.

Prescribe

CORGARD®

nadolol tablets

40 mg, 80 mg, 120 mg, and 160 mg tablets

The common-sense beta-blocker for angina pectoris

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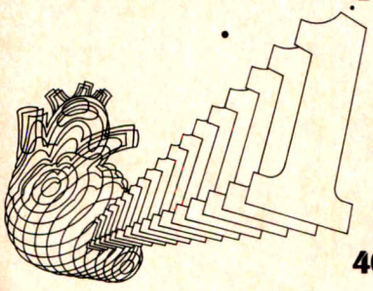
See next page for brief summary.

The only once-a-day beta-blocker for both angina pectoris and hypertension



CORGARD®
nadolol tablets

40 mg, 80 mg, 120 mg, 160 mg scored tablets

CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure—Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal — Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) — PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery — Because beta-blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia — Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis — Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function — Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients — Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions — Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility — In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy — In animal reproduction studies with nadolol, evidence of embryo- and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers — It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use — Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular — Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System** — Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory** — Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal** — Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous** — Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System** — reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal** — mesenteric arterial thrombosis; ischemic colitis. **Hematologic** — agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic** — fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous** — reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia — Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure — Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension — Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm — Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 1(mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval — see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® single-dose packs of 100 tablets.

Reference:

1. Data on file, Squibb Institute for Medical Research.

SQUIBB

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Issued: January 1981

511-515

INTRODUCING THE VARIAN V-3400R

The Best Buy in Ultrasound Sector Scanning

New and improved features and a capacity for integrating future developments make the new Varian V-3400R phased array sector scanner the best buy in cardiac ultrasound imaging.

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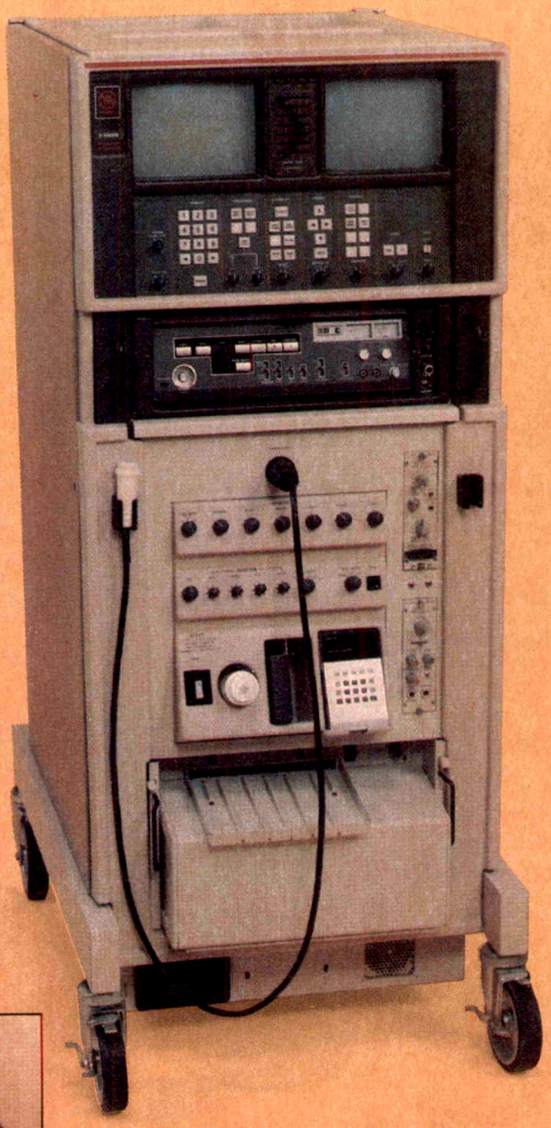

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Built-in capacity for integrating future Varian developments now in progress such as: Digital M-Mode, Dual-Phasing High-Resolution Image Processing, and Doppler.

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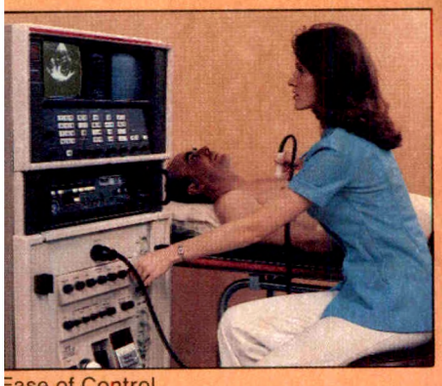
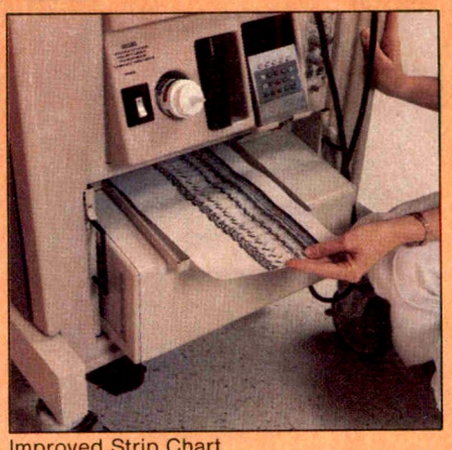


Ease of Control



Improved Strip Chart

Mobility

708 **Prolapsed Left Atrium Behind the Left Ventricular Posterior Wall: Two Dimensional Echocardiographic and Angiographic Features**

WILLIAM C. REEVES, THOMAS CIOTOLA, JOSEPH D. BABB, EDWARD BUONOCORE, DAVID LEAMAN with the technical assistance of EUGENE BEERS and LaDORA PAPICH

In three patients with a greatly enlarged left atrium resulting from rheumatic mitral valve disease, two dimensional echocardiography correctly detected portions of a huge left atrium that prolapsed behind the left ventricular posterior wall and mimicked an isolated posterior pericardial effusion on M mode echocardiography. In one patient left ventricular angiography suggested a ventricular septal defect or a false aneurysm of the left ventricle in the single plane right anterior oblique projection. For these reasons the authors urge the use of two dimensional echocardiography in the presence of a large left atrium to look for left atrial prolapse when isolated echo-free spaces are noted behind the left ventricular posterior wall on M mode echocardiography. All three patients underwent successful mitral valve replacement.

BETHESDA CONFERENCE REPORT

713 **Eleventh Bethesda Conference: Prevention of Coronary Heart Disease**

This Bethesda Conference focuses on the role of physician leadership in the prevention of coronary heart disease. The speakers reiterate the importance and potential value of weight control, dietary management, lowering of elevated blood pressure, cessation of cigarette smoking and avoidance of excessive alcohol consumption in improving the chances of avoiding clinical coronary artery disease. Changes in lifestyle and lifestyle-related risk factors have made a key contribution to the appreciable decline in mortality due to coronary artery disease. More is possible and needed.

SPECIAL DEPARTMENTS

777 **Education Update**

786 **American College of Cardiology News**

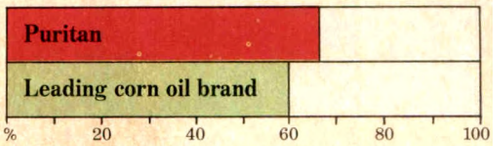
Puritan® Oil–a proven ingredient of cholesterol management

While the etiology of atherosclerosis and coronary heart disease involves many factors..."Cholesterol seems to be the thread running through the web of circumstances culminating in a clinical atherosclerotic event."*
A diet that includes Puritan Oil has been clinically proven effective in reducing serum cholesterol.

Puritan® Oil–superior in polyunsaturates to corn oil

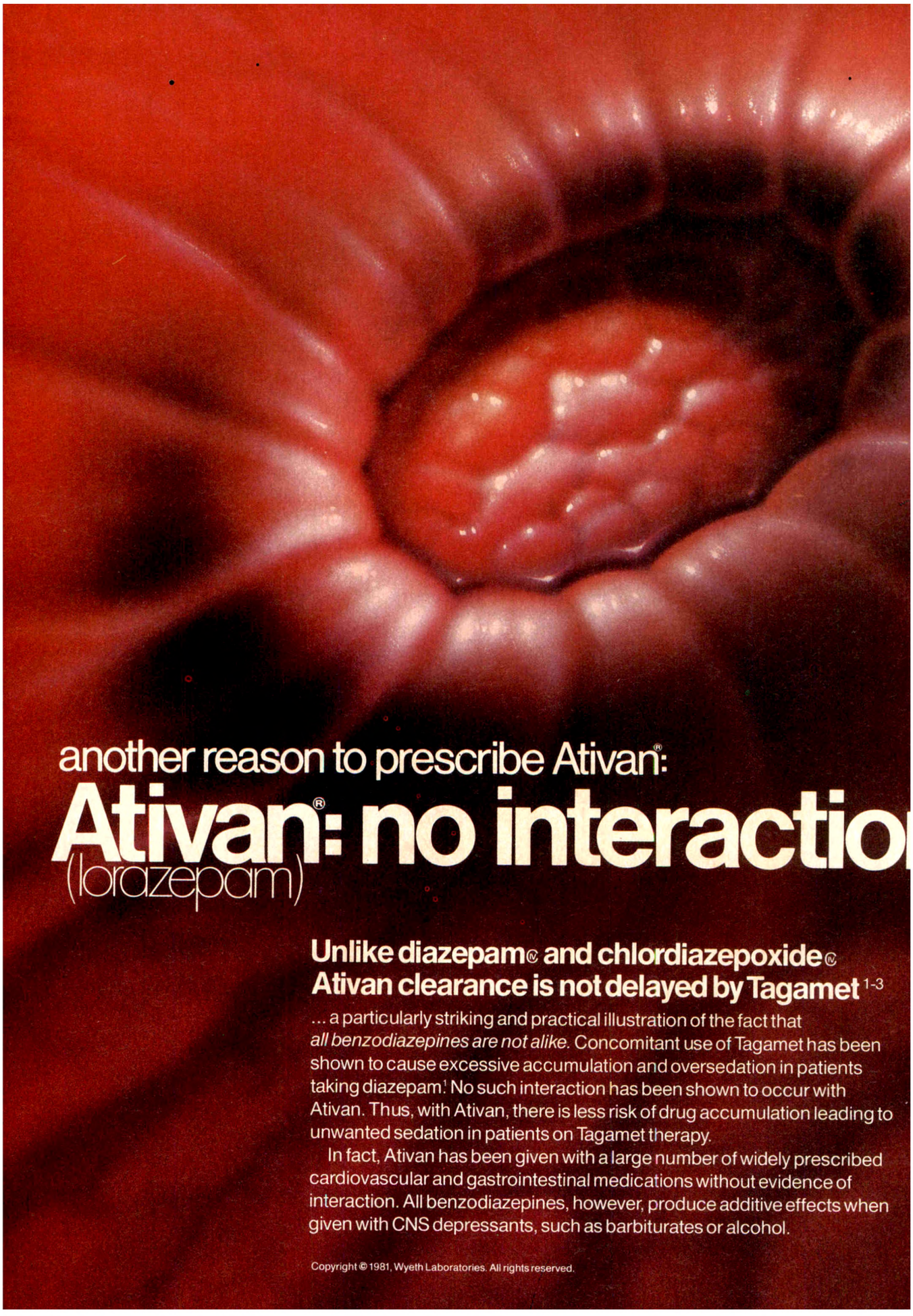
Puritan Oil is made principally from highly polyunsaturated sunflower oil. Puritan provides polyunsaturate levels superior to those of corn oil, the previous standard in a cholesterol-management diet.

A comparison of polyunsaturate levels



Unsurpassed culinary appeal helps encourage patient compliance
Light taste and unsurpassed culinary performance encourage patient compliance in successful long-term dietary management.

*Kannel, W.B.: The role of cholesterol in coronary atherogenesis, Med. Clin. North Am. 58:363-379, 1974.


another reason to prescribe Ativan®:
Ativan®: no interactio
(lorazepam)
Unlike diazepam® and chlordiazepoxide®
Ativan clearance is not delayed by Tagamet[1-3]
... a particularly striking and practical illustration of the fact that *all benzodiazepines are not alike.* Concomitant use of Tagamet has been shown to cause excessive accumulation and oversedation in patients taking diazepam.[1] No such interaction has been shown to occur with Ativan. Thus, with Ativan, there is less risk of drug accumulation leading to unwanted sedation in patients on Tagamet therapy.
In fact, Ativan has been given with a large number of widely prescribed cardiovascular and gastrointestinal medications without evidence of interaction. All benzodiazepines, however, produce additive effects when given with CNS depressants, such as barbiturates or alcohol.
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with Tagamet®*

Other advantages of Ativan (lorazepam):

- Shorter half-life helps avoid excessive accumulation
- No active metabolites, less work for the liver
- B.I.D. dosage encourages compliance

Ativan® for (lorazepam) Anxiety

References:
1. Klötz U, Reimann I: N Engl J Med *302*:1012-1014, 1980.
2. Desmond PV, Patwardhan RV, Schenker, S, et al: Ann Intern Med *93*:266-268, 1980.
3. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.

*Tagamet (cimetidine) is a registered trademark of Smith Kline & French Laboratories, Division of SmithKline Corporation.

†Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic.

See important information on following page.

Wyeth Laboratories
Philadelphia, PA 19101

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

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Dosage: **Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.**

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THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
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Every cardiologist, internist, pediatrician, surgeon—indeed *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons wl this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, thi book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdc here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

Thomas N. James, MD
The Mary Gertrude Waters Professor of Cardiology and Chairman the Department of Medicine, The University of Alabama in Birmin ham, and Physician-in-Chief, University of Alabama Hospitals.

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1. Congestive heart failure: Congestive heart failure, all degrees, is the primary indication. The increased cardiac output due to digoxin results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digoxin, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digoxin should be continued after heart failure is abolished unless some known precipitating factor is corrected.

2. Atrial fibrillation: Atrial fibrillation, especially when the ventricular rate is elevated. Digoxin rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concomitant congestive failure ameliorated. Digoxin should be continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. Atrial flutter: Digoxin slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digoxin at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digoxin if failure ensues or if atrial flutter is a frequent occurrence.

4. Paroxysmal atrial tachycardia: Oral digoxin may be used, especially if the condition is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if heart failure has ensued or paroxysms recur frequently, digoxin should be maintained by oral administration.

Digoxin is not indicated in sinus tachycardia unless due to heart failure.

5. Cardiogenic shock: The drug is often employed, especially when the condition is accompanied by pulmonary edema. Digoxin seems to affect adversely shock due to septicemia from gram-negative bacteria.

CONTRAINDICATIONS: The presence of toxic effects (see ADVERSE REACTIONS section) induced by any digitalis preparation is a contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations, and another may be tried.

Ventricular fibrillation.

WARNINGS:

> Digitalis alone or with other drugs has been promoted for use in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs in the treatment of obesity is dangerous.

Many of the arrhythmias for which digoxin is advised closely resemble those reflecting digoxin intoxication. If the possibility of digoxin intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digoxin intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency require smaller than usual doses of digoxin. Newborn infants display considerable variability in their tolerance to digoxin, depending on their degree of maturity.

Premature and immature infants are particularly sensitive, and dosage must be reduced and digitalization should be even more individualized and cautiously approached than in more mature infants. Impaired renal function must also be carefully taken into consideration.

Congestive heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. A relatively low total dose administered in divided doses and concomitant use of antihypertensive drugs has been recommended. ECG monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with rheumatic carditis, especially when severe, are unusually sensitive to digoxin and prone to disturbances of rhythm. If heart failure develops, digitalization may be initiated with relatively low doses; then it can be cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS: Atrial arrhythmias associated with hypermetabolic states are particularly resistant to digoxin treatment. Care must be taken to avoid digoxin toxicity if digoxin is used to help the arrhythmia.

Digoxin is not indicated for the treatment of ventricular tachycardia unless congestive heart failure supervenes after a protracted episode not itself due to digoxin.

Potassium depletion sensitizes the myocardium to digoxin and toxicity may develop even with usual dosage. Hypokalemia may also alter the rate of onset and intensity of the positive inotropic effect of digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin.

Potassium wastage may result from diuretic or corticosteroid therapy, hemodialysis, and from suction of gastrointestinal secretions. It may accompany malnutrition, diarrhea, prolonged vomiting, old age, and long-standing congestive heart failure. In general, rapid changes in serum potassium or other electrolytes are to be avoided, and intravenous treatment with potassium should be reserved only for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES section).

Patients with acute myocardial infarction, severe pulmonary disease, or far advanced heart failure may be more sensitive to digoxin and more prone to disturbances of rhythm.

Calcium affects contractility and excitability of the heart in a manner similar to that of digoxin. Calcium may produce serious arrhythmias in digitalized patients.

In myxedema, the digoxin requirements are less because excretion rate is decreased and blood levels are significantly higher.

In incomplete A-V block, especially in patients subject to Stokes-Adams attacks, advanced or complete heart block may develop if digoxin is given. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

Patients with chronic constrictive pericarditis may respond unfavorably to digoxin.

Patients with idiopathic hypertrophic subaortic stenosis must be managed extremely carefully. Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Renal insufficiency delays the excretion of digoxin and dosage must be adjusted accordingly in patients with renal disease. Note: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require reduction of digoxin dosage.

Dosage must be carefully titrated and differences in the bioavailability of parenteral preparations, elixirs, and tablets should be taken into account when switching patients from one preparation to another.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

ADVERSE REACTIONS:

Gynecomastia: Uncommon.

Overdose or toxic effects in adults:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea are the most common early symptoms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms.

Central nervous system: Visual disturbances (blurred vision, yellow vision), headache, weakness, apathy.

Cardiac disturbances (arrhythmias): Ventricular premature beats are the most common, except in infants and young children. Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (interference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digoxin overdosage.

Conduction disturbances: Excessive slowing of the pulse is a clinical sign of digoxin overdosage. Atrioventricular block of increasing degree may proceed to complete heart block. Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac toxic disturbances. Digoxin may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

Overdose or toxic effects in children:

Toxic signs differ from the adult in a number of respects. Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and visual disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms, and paroxysmal atrial tachycardia with A-V block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGE: Digoxin should be discontinued until all signs of toxicity are abolished. Discontinuation may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided oral doses totaling 4-6 grams for adults (see PEDIATRIC INFORMATION section for pediatric dosage) may be given provided renal function is adequate.

When correction of the arrhythmia is urgent and the serum potassium level is low or normal, potassium should be administered intravenously in a solution of 5 percent dextrose in water. A total of 40-100 milliequivalents (30 milliequivalents per 500 milliliters) is given at the rate of 20 milliequivalents per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Continuous electrocardiographic monitoring should be performed to watch for any evidence of potassium toxicity, e.g., peaking of T waves, and to observe the effect on the arrhythmia so that the infusion may be promptly stopped when the desired effect is achieved.

Caution: Potassium should not be used and may be dangerous for severe or complete heart block due to digoxin and not related to any tachycardia.

Other agents that have been approved for the treatment of digoxin intoxication include procainamide, lidocaine, and propranolol.

Pediatric Information: (See adult section for other recommendations for the treatment of arrhythmias produced by overdosages and for additional recommendations and cautions regarding the use of potassium.) Potassium preparations may be given orally in divided doses totaling 1-1.5 milliequivalents/kilogram (1 gram K contains 13.4 milliequivalents). When correction of the arrhythmia is urgent, approximately 0.5 milliequivalents/kilogram of potassium per hour may be given, with careful electrocardiographic monitoring, as a solution of 20 milliequivalents or less for 500 milliliters in 5 percent dextrose in water. The total dose should generally not exceed 2 milliequivalents of potassium/kilogram.

DOSAGE AND ADMINISTRATION: Oral digoxin is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the lean body mass of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures that may require considerable modification as dictated by individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended or average doses. (See WARNINGS and PRECAUTIONS sections.)

The average amount of digoxin that patients must accumulate to be digitalized with digoxin tablets is 1.0-1.5 milligrams. Digitalization may be accomplished by any of several approaches that vary in dosage and frequency of administration, but reach the same endpoint in terms of total amount accumulated.

In previously undigitalized patients, a single loading dose of 0.5-0.75 milligram orally usually produces a detectable effect in 1-2 hours that becomes maximal in 6-8 hours. Additional doses of 0.25-0.5 milligram may be given cautiously at 6-8 hour intervals to full digitalization.

In previously undigitalized patients, institution of daily maintenance therapy (0.125-0.5 milligram, see next paragraph) without a loading dose results in development of steady-state plateau concentrations in about 7 days in patients with normal renal function.

The average daily oral maintenance dose is 0.125-0.5 milligram, usually 0.25 milligram. In the elderly patient, 0.125-0.25 milligram should be considered the average maintenance dose.

In patients with renal impairment, digoxin excretion is impaired and serum half-life is prolonged. Digitalizing and maintenance doses are lower than those recommended for patients with normal renal functions. Signs of digoxin toxicity develop sooner in patients with renal impairment, and it takes longer for toxic signs and symptoms to disappear. Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state plateau in patients with renal impairment than in patients with normal renal function.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

Children: Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive, requiring reduced dosage that must be determined by careful titration.

Oral Dosage. Beyond the immediate newborn period, children require proportionally greater doses than adults on the basis of body weight or surface area. The recommended oral digitalizing dosages in children with normal renal function are:

Newborn infants (normal), up to 1 month, require 40-60 micrograms (mcg)/kilogram.

Infants, 1 month to 2 years, require approximately 60-80 micrograms (mcg)/kilogram.

Children, 2 years to 10 years, require 40-60 micrograms (mcg)/kilogram.

Children, over 10 years of age, require adult dosages in proportion to their body weight.

Maintenance therapy is 20-30 percent of the digitalizing dose administered each day.

Long term use of digoxin is indicated in almost all infants who have been digitalized for acute congestive heart failure unless the cause is transient. Many favor maintaining digoxin until at least 2 years of age in all infants with paroxysmal atrial tachycardia or in those who show either definite or latent failure.

Many children with severe inoperable congenital defects need digoxin throughout childhood and often for life.

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CLINICAL STUDIES

The Natural History of Idiopathic Dilated Cardiomyopathy

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Between 1960 and 1973, a total of 104 patients at the Mayo Clinic had a diagnosis of idiopathic dilated cardiomyopathy on the basis of clinical and angiographic criteria; these patients were followed up for 6 to 20 years. Twenty-one percent of the patients had a history of excessive consumption of alcohol, 20 percent had had a severe influenza-like syndrome within 60 days before the appearance of cardiac manifestations and 8 percent had had rheumatic fever without involvement of cardiac valves several years before; thus, possible etiologic risk factors of infectious-immunologic type may be important. Eighty patients (77 percent) had an accelerated course to death, with two thirds of the deaths occurring within the first 2 years. Twenty-four patients (23 percent) survived, and 18 of them had clinical improvement and a normal or reduced heart size. Univariate analysis at the time of diagnosis revealed three factors that were highly predictive ($p < 0.01$) of the clinical course: age, cardiothoracic ratio on chest roentgenography and cardiac index. Systemic emboli occurred in 18 percent of the patients who did not receive anticoagulant therapy and in none of those who did; thus, anticoagulant agents should probably be prescribed unless their use is contraindicated.

Recognition of the protean manifestations of cardiomyopathy has led to the modification of previous definitions. Currently, cardiomyopathies are defined as "heart muscle diseases of unknown cause." [1] On the basis of the morphologic and functional abnormalities, Goodwin[2] classified cardiomyopathies into three major groups: congestive, hypertrophic and restrictive or obliterative.

The term *congestive cardiomyopathy* is derived from the common late clinical manifestation of congestive cardiac failure. However, dilatation of the cardiac chambers (particularly the left ventricle) is an earlier and predominant feature, and for this reason the term *dilated cardiomyopathy* is preferred.[1] Idiopathic dilated cardiomyopathy remains a challenge because the cause is unknown, the natural history is ill defined, and the response to therapy is generally unsatisfactory. A need for new preventive and therapeutic approaches to this commonly fatal disease is obvious. Identification of the patients most likely to benefit from newer therapeutic advances requires an understanding of the natural history of the disease. Accordingly, this long-term retrospective follow-up study was undertaken.

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Methods

Study patients: The study group comprised 104 patients (64 men and 40 women; median age 49 years) with dilated cardiomyopathy who were seen consecutively at the Mayo Clinic between January 1960 and December 1973. All 104 patients were followed up for a minimum of 6 years or until death, if it occurred in less than 6 years. The median follow-up period was 11 years and the longest was 20 years. The initial clinical history of the 104 patients was recorded by at least two physicians, and the clinical records were carefully examined in retrospect by two of us. Follow-up information was obtained in all patients from repeated examinations at the Mayo Clinic (91 percent of patients) and from responses to telephone calls to the patients or relatives and to the referring physicians. Although the study originally included 125 patients, the 21 patients living outside the United States were excluded because complete information was difficult to obtain. At the time of entry into the study, all patients had a diagnosis of dilated cardiomyopathy that fulfilled strict clinical, angiographic and etiologic criteria, as described in the following sections.

Clinical criteria: At the time of entry into the study, each of the 104 patients had two or more of the following four clinical features: (1) symptoms and signs of left or right heart failure, or both; (2) roentgenographic evidence of cardiomegaly and a cardiothoracic ratio greater than 0.50; (3) an electrocardiographic abnormality in the form of left ventricular conduction delay (with a wide QRS complex greater than 0.08 second), first degree atrioventricular block (P-R interval greater than 0.19 second), intraatrial conduction delay (P wave greater than 0.10 second), left ventricular hypertrophy (S wave in lead V_1 or V_2 plus R wave in lead V_5 or V_6 greater than 40 mm) or atrial flutter or fibrillation; and (4) a history of systemic emboli since the time of initial manifestation of the disease. Patients with clinical evidence of underlying coronary artery disease, systemic hypertension (hypertension subsequently developed in only four patients), cor pulmonale, valvular heart disease, predominant pericardial disease, and insulin-dependent diabetes or systemic disease involving the heart muscle were excluded from the study.

In all patients we recorded (1) the period between the initial clinical manifestation and the clinical and angiographic diagnosis of dilated cardiomyopathy or entry into the study, (2) all clinical features at the time of the diagnosis or entry into the study, and (3) all clinical features during the total follow-up period, including the exact period during which anticoagulant agents and other therapeutic interventions were used.

Hemodynamic and angiographic criteria: At the time of entry into the study, all 104 patients underwent left ventricular hemodynamic and angiographic study and 46 patients also had selective coronary cineangiography.[3] At the time of catheterization, most patients (85 percent) were taking digoxin or diuretic drugs, or both. Catheterization procedures included (1) measurement of left ventricular end-diastolic pressure and cardiac index, (2) left ventriculography, and (3) coronary cineangiography. When these studies were done (1960 to 1973), left ventricular ejection fraction could not be accurately obtained because simultaneous biplane views were not available; in addition, the 6 inch (15.24 cm) frame used at that time was often too small to assess the larger ventricles.

The cardiac index was determined[4] with use of the oxymetric principle of Fick in 63 patients, the Peterson-Wood indicator-dilution technique with indocyanine green in 21 patients and with both methods in 20 patients; this procedure provided paired results that did not differ statistically.

Left ventriculography was performed in the 45° right anterior oblique projection. The left ventricular anterior surface (which included the anterobasal, anterolateral and apical segments) and the inferior surface (which included the diaphragmatic and posterobasal segments) were analyzed for distinct types of abnormal contraction, as described by Herman et al.[5] As required for inclusion in the study, in all patients the left ventricular angiogram revealed a dilated left ventricle and a diffuse, global decrease in amplitude of contraction, a feature that contrasts with the segmental wall motion abnormalities of coronary heart disease.

Coronary cineangiograms were performed in right and left oblique and left lateral projections, and the degree of obstruction of a vessel was derived from estimates of the width of the respective vessel in its normal portion compared with that of its most diseased portion, the latter being expressed as a percent of the former. Patients were excluded from the study if they had an obstruction of at least 50 percent of luminal diameter in one of the four major coronary arteries (right coronary, left anterior descending, left circumflex and left main coronary) or of their main branches. On the basis of these criteria, the 46 patients who had selective coronary cineangiography were free of appreciable coronary artery disease; moreover, 14 other patients of the group who had postmortem examination were also free of appreciable coronary artery disease. Thus, as required for inclusion in the study, none of the 104 patients had clinical evidence of appreciable coronary artery disease, and this was confirmed in 60 of the patients by coronary cineangiography or autopsy; this group of 60 also included the 8 who had abnormal Q waves in the electrocardiogram that were otherwise atypical of myocardial infarction.

Etiologic criteria: Because cardiomyopathies are defined as diseases of the cardiac muscle of unknown cause, we excluded all patients with specific disorders involving heart muscle as part of a general systemic disease.[1,6] Moreover, in the 39 autopsy cases, neither gross pathologic study nor light microscopy offered any clue about cause.

In an attempt to determine possible risk factors that might disclose the underlying cardiomyopathy or contribute to its development, we computed and analyzed the following factors: (1) 52 professional and possible environmental factors (Hollingshead Occupational and Educational Scales Code, U.S. Federal Government, 1958) (patients living outside the United States were excluded from the study); (2) excessive consumption of alcohol, defined as a daily intake of at least 8 ounces of hard liquor or 2 quarts of beer for the preceding 10 years (no patient in the study had consumed excessive amounts of wine, that is, more than 1 quart daily); (3) severe influenza-like syndrome, associated or unassociated with pneumonitis, occurring 2 to 8 weeks before the first manifestation of cardiomyopathy; (4) clinical evidence of rheumatic fever[7] without apparent cardiac involvement, occurring several years before the first manifestation of the cardiomyopathy; (5) first manifestation of cardiomyopathy within 6 weeks after childbirth; and (6) family history, defined as documented dilated cardiomyopathy in at least one first degree relative.

Statistics: Significance of univariate analysis of prognostic factors was tested with Student's t test or the chi-square test. Stepwise linear discriminant function analysis was carried out according to the BMD P7M computer program of the Health Sciences Computing Facility, University of California, Los Angeles, California.

Results

Clinical and Hemodynamic Features

Clinical manifestations: The median period between the initial clinical manifestation and the clinical and angiographic diagnosis of dilated cardiomyopathy or entry into the study was 1.3 years. In decreasing order

TABLE I.

Clinical Features

	At Diagnosis (%)	At Follow-Up (%)
Cardiomegaly	87	89
Electrocardiographic abnormality	80	87
Left ventricular conduction delay	36	51
Atrial flutter or fibrillation	19	23
Intraatrial conduction delay	17	25
Left ventricular hypertrophy	14	7
First degree atrioventricular block	11	39
Heart failure	73	96
Systemic emboli	4	18

of frequency, the clinical manifestations at the time of diagnosis or entry into the study (Table I) were roentgenographic evidence of cardiomegaly (87 percent); an electrocardiographic abnormality (80 percent), most frequently in the form of left ventricular conduction delay; symptoms of cardiac failure (73 percent), and systemic emboli (4 percent). During the follow-up period, the frequency of these clinical manifestations, particularly cardiac failure and systemic emboli, increased.

With respect to systemic emboli (Table II), 103 patients were not taking anticoagulant agents during some period of the study; 23 episodes of systemic emboli occurred during this time in 19 patients (18 percent of this group). Of the patients with systemic emboli, 16 had one embolic episode, 2 had two episodes, and 1 had three episodes. After the initial clinical manifestation of dilated cardiomyopathy, 12 of the embolic episodes occurred in the 1st year, 5 between 2 and 4 years, 3 between 5 and 9 years, and 3 after 10 or more years. Thirty-two patients were taking anticoagulant agents during some period; no systemic emboli developed during this time. Because the years of exposure were greater for the group not taking than for the group taking anticoagulant therapy, statistical analysis incorporated the number of embolic events per 100 patients per year of exposure. Approximately four embolic events per 100 patient-years occurred in the group without anticoagulant therapy and none in the group with such therapy ($p < 0.05$). A second predisposing factor for systemic emboli appeared to be the presence of atrial fibrillation (Table II). Systemic emboli developed in 33 percent of the patients who had atrial fibrillation, but in only 14 percent of patients without atrial fibrillation; however, this difference did not reach statistical significance. There were no additional clinical or hemodynamic variables that were predictors of systemic embolism.

TABLE II

Systemic Emboli

	Patients With Emboli		Patient-Years of Exposure	Events per 100 Patient-Years (n)
	n	%		
Treatment with anticoagulant agents				
Yes (n = 32)	0	0	101	0
No (n = 103)	19	18	624	3.5
Atrial fibrillation				
Yes (n = 24)	8	33	. . .	. . .
No (n = 80)	11	14	. . .	. . .

Hemodynamic features: Cardiac hemodynamic evaluation at the time of diagnosis revealed a left ventricular end-diastolic pressure greater than 15 mm Hg in 81 patients (78 percent) and a cardiac index of less than 2.5 liters/min per m^2 in 65 patients (62 percent). One or the other abnormality was found in 96 patients (92 percent).

Clinical Course and Prognosis

At the time of the last follow-up analysis, 80 patients (77 percent) had died, and the majority of deaths (two thirds) occurred within the first 2 years (Fig. 1). The survival curve for the 24 remaining patients (23 percent) was comparable with that of the control group matched for age and sex. In the 24 living patients, chest roentgenograms were obtained both at the time of diagnosis and at the time of the last follow-up examination. Of these patients, 17 had a cardiothoracic ratio greater than 0.50, whereas at the time of the last follow-up analysis, 18 patients had either a normal or decreased cardiac size compared with the initial assessment (Fig. 2). In addition, comparison of the symptoms with those present at the time of diagnosis showed that only 3 of the 24 patients had had subjective deterioration and all of the others had had improvement or no change in symptoms.

Univariate analysis of prognostic factors: Because all patients were followed up for at least 6 years and most deaths occurred within that time, we evaluated the prognostic factors for the 6 year clinical course. Evalu-

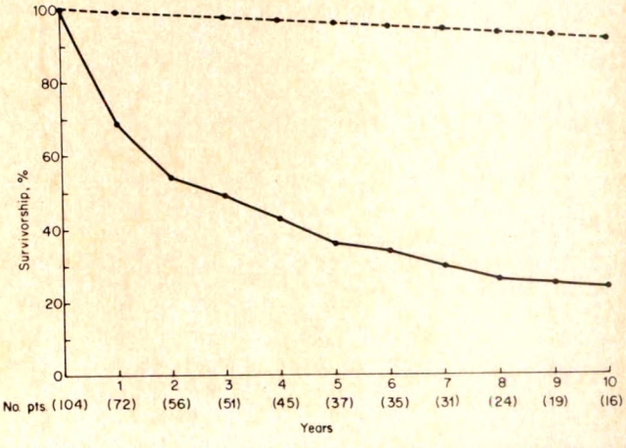

FIGURE 1. Observed survival plotted against time in years in 104 patients (pts.) with the diagnosis of idiopathic dilated cardiomyopathy (**solid line**). The **dashed line** represents the control expected survival, on the basis of age and sex distribution, according to the death rates of the Minnesota 1970 White Population Life Table. The number of alive patients under observation at each follow-up interval is indicated in parentheses.

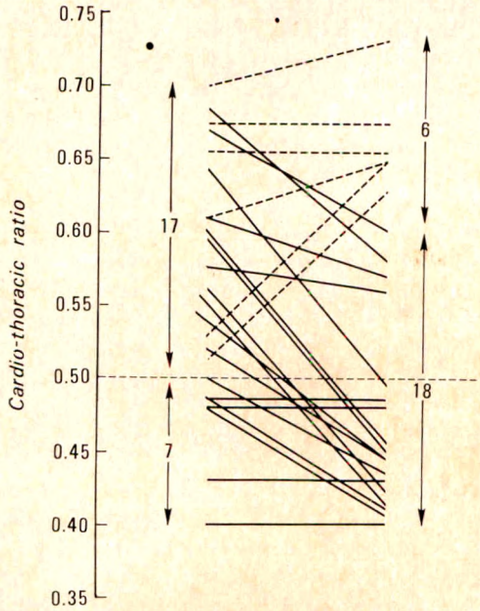

FIGURE 2. Roentgenographic cardiothoracic ratio at the time of diagnosis (**left end of lines**) and at the time of last follow-up examination (**right end of lines**) (median interval 10 years) in the 24 living patients. The **solid lines** represent patients who had a normal or reduced cardiac size at last follow-up analysis; the **dashed lines** represent those in whom the degree of cardiomegaly remained unchanged or had progressed.

ation at the time of diagnosis revealed only four factors that were independently and significantly predictive (Table III): (1) Age of the patient. The older the patient, the higher the probability of death; we arbitrarily chose age 55 years as a good discriminative age because patients aged 55 years or older had a mortality rate of 97 percent. (2) Cardiothoracic ratio calculated from the chest roentgenogram. The higher the cardiothoracic ratio, the higher the probability of death; arbitrarily, we selected 0.55 as a good discriminative cardiothoracic ratio, inasmuch as the mortality was 86 percent in patients with a ratio of 0.55 or more but only 40 percent in patients with a ratio of less than 0.55. (3) Cardiac index. The lower the cardiac index, the higher the probability of death; arbitrarily, we chose 3 liters/min per m^2 as a good discriminative cardiac index because the mortality rate was 89 percent in patients with a lower cardiac index but only 35 percent in those with an index of 3 liters/min per m^2 or greater. (4) Increased left ventricular end-diastolic pressure. The higher the pressure, the higher the probability of death; we arbitrarily chose 20 mm Hg as a good discriminative value because the mortality rate was 87 percent in patients with a pressure of 20 mm Hg or higher.

TABLE III

Prognostic Factors

Factors	p Value*	Division Point†	Dead (%)	Alive (%)
Age (yr)	<0.01	≥55	97	3
		<55	66	34
Cardiothoracic ratio	<0.01	≥0.55	86	14
from chest roentgenogram		<0.55	40	60
Cardiac index	<0.001	<3.0	89	11
(liters/min per m^2)		≥3.0	35	65
LVEDP (mm Hg)	<0.05	≥20	87	13
		<20	63	37

* Univariate analysis, level of significance. † Arbitrarily chosen. LVEDP = left ventricular end-diastolic pressure; p = probability

Linear discriminant analysis of prognostic factors: Stepwise linear discriminant function analysis of all the prognostic factors at the time of diagnosis (age, cardiothoracic ratio, cardiac index and left ventricular end-diastolic pressure) showed that with the combination of cardiac index and cardiothoracic ratio, 86 percent of the patients could be correctly classified with respect to 3 year survival.

Possible Etiologic or Risk Factors

In an attempt to determine risk factors that might disclose the underlying cardiomyopathy or contribute to its development, we found, in decreasing order of frequency, the following factors, singly or in combination: (1) excessive consumption of alcohol (21 percent of the patients); (2) a severe influenza-like syndrome shortly before the first clinical manifestation of cardiomyopathy (20 percent; the syndrome recurred in only two of these patients); (3) a clinical history of rheumatic fever, without apparent involvement of the cardiac valves, 15 to 35 years before the first clinical manifestation of cardiomyopathy (8 percent); (4) postpartal cardiomyopathy (3 percent; none of these patients and only one in the total group had a repeated pregnancy); and (5) familial cardiomyopathy (2 percent). In 49 percent of the patients, no apparent risk factors were found.

Statistical analysis of the presence or absence of each of these risk factors revealed no prognostic significance. However, among the 22 patients with excessive consumption of alcohol, all 4 patients who are alive have completely abstained from alcohol, compared with only 8 of the 18 patients who died. This difference was not statistically significant.

Discussion

This review, which is primarily a study of the natural history of idiopathic dilated cardiomyopathy, is unique. The study group consists of a medical series in which the diagnosis was confirmed at cardiac catheterization in all patients and in which the duration of follow-up analysis is the longest thus far reported.

Problems in Selection of Patients

Two aspects underlying the selection of these patients should be emphasized.

1. The number of patients entered into this study during the 14 year period (1960 through 1973) was relatively small (104 patients) even though the incidence of this disease appears to be high.[8] This analysis is retrospective, and a prerequisite for entry was ventriculographic evidence of cardiomyopathy. In the early 1960s, cardiac catheterization was less commonly per-

formed than in the 1970s, thus limiting the patient population potentially available for inclusion in the study. Consequently, the study group is highly selected but well defined.

2. In 44 of the 104 patients, the coronary anatomy was not defined by arteriography or at autopsy. However, significant coronary artery disease was highly unlikely in these patients for the following reasons: First, none had clinical, electrocardiographic or ventriculographic features of coronary artery disease. Second, the natural history of these patients was almost identical with that of the 60 patients in whom the absence of appreciable coronary artery disease was proved at arteriography or autopsy, and both groups had similar clinical, electrocardiographic and ventriculographic features. These findings strongly suggest that the 44 patients did not have significant coronary artery disease or "ischemic cardiomyopathy," [9] although this cannot be categorically excluded.

Clinical and Hemodynamic Features

Our study and others[8,10,11] show that features of left- or right-sided heart failure are not necessarily the initial clinical manifestations of the disease. The term *dilated cardiomyopathy* aptly describes the initial ventriculographic features of left ventricular dilatation and a diffuse, global decrease in amplitude of contraction. Nevertheless, perhaps in the future, identification before the development of ventricular dilatation, either clinically,[12] echocardiographically[13,14] or radioisotopically,[15,16] will enable earlier and possibly more successful therapeutic intervention.

This and other studies[11,17–21] illustrate that during the later stages of the disease, heart failure, cardiomegaly and electrocardiographic abnormalities almost invariably occur. Hemodynamic correlates were identified by cardiac catheterization in that almost all of the patients had a high left ventricular end-diastolic pressure and a low cardiac index. By definition, left ventriculograms were abnormal in all patients, revealing a global decrease in contractility suggestive of generalized myocardial involvement.

Systemic embolism: The large incidence of systemic emboli found in our patients is a well established clinical observation.[8,10,17–19,22] Autopsy studies have demonstrated that such emboli arise from a thrombus attached to the underlying diseased left ventricular endocardium[8,17,19,22] or, in some cases, from a left atrial thrombus.[17] In our patients we noted that over half of the systemic embolic episodes occurred within the 1st year of the initial clinical manifestation of cardiomyopathy and, although the total incidence decreased with time, this appeared to be mostly a function of the decreasing number of surviving patients.

Role of atrial fibrillation and anticoagulant therapy: Univariate analysis of the various hemodynamic and clinical features revealed that only the presence of atrial fibrillation appeared to show some predictive value for systemic emboli. However, the 32 patients who received anticoagulant therapy had no systemic embolic episodes during the period of anticoagulation. This finding, which was statistically significant, appears to be of great therapeutic relevance. That is, it suggests that in patients with dilated cardiomyopathy, oral administration of anticoagulant agents may help prevent systemic embolism. Our current policy is to prescribe long-term anticoagulant therapy in all of these patients unless a specific contraindication exists. None of our patients who were treated with anticoagulant agents had major hemorrhagic complications.

Clinical Course and Prognosis

This group of patients with dilated cardiomyopathy had either an accelerated course to death (77 percent of patients) or a striking improvement or stabilization (23 percent). Thus, of the patients who died, two thirds died within the first 2 years after diagnosis. In contrast, the condition of most remaining patients has subjectively improved or stabilized and, their heart size is normal or smaller.

The strikingly different prognoses in these two patient groups could reflect the specific nature and severity of the initial cardiac insult and its "tolerance" by the heart. Our data conform with those of others[8,10,11,21–23] suggesting that the more severe the clinical and hemodynamic manifestations at the time of diagnosis, the worse is the long-term prognosis. Not surprisingly, a severe initial cardiac insult with its attendant consequences of substantial cardiomegaly, low cardiac index and high left ventricular end-diastolic pressure does identify a group of patients with an unfavorable outcome leading to early death.

Kristinsson,[11] in a shorter follow-up analysis of patients seen at the Hammersmith Hospital in London, also noted a high mortality rate within the first 2 years after the clinical diagnosis. Recently, Segal et al.[10] recorded a less dramatic initial mortality rate. Their patient population differed from ours in that it was highly selected, excluding patients with excessive alcohol intake, possible viral myocardial disease or viral myopericarditis and those with peripartal cardiomyopathy. Furthermore, because diagnostic cardiac catheterization was not a specific requirement in their study, many of the inpatients did not fulfill our stringent hemodynamic and angiographic criteria for cardiomyopathy. Since in our study most patients were treated with digoxin or diuretic agents or both, the prognostic value of such treatment could not be analyzed. In addition, because only patients seen between 1960 and 1973 were entered into the study, the new approach of afterload reduction with vasodilating agents could not be assessed.

Etiologic and Therapeutic Considerations

Because the definition of idiopathic dilated cardiomyopathy is "heart muscle disease of unknown causes," a semantic argument is introduced when potentially etiologic agents are discussed. Once the cause of a specific form of cardiac muscle disease is established, on the basis of this definition, the term *cardiomyopathy* should no longer be used. In agreement with Goodwin,[6] we believe that idiopathic dilated cardiomyopathy is

probably the result of several factors acting in concert in a susceptible person. Thus alcohol, viral infections, puerperium and other conditions should currently be regarded only as possible risk factors; whether these conditions potentiate the underlying cardiomyopathy, unmask it or act as causative agents in their own right is unclear. In most cases, neither light microscopy nor ultrastructural studies identify a single causative agent.[6,24]

Alcohol: A link between excessive alcohol intake and cardiomyopathy has been alluded to frequently in the past,[24–28] but its precise role or mechanism of action is not fully understood.[27,28] In 21 percent of our patients, we identified an excessive consumption of alcohol according to criteria defined by others.[25,27,29–32] Our findings support previous observations[32,33] that alcohol may be deleterious in any patient with cardiomyopathy and that complete abstinence from alcohol may be beneficial in some patients. Whether alcohol acts as a primary causative agent cannot be established from our data, but it appears that in the presence of diffuse myocardial disease, alcohol is an added insult best avoided.

Viral infection: It is tempting to incriminate viral infection as a cause of cardiomyopathy. Twenty percent of our patients had a severe influenza-like syndrome shortly before the first manifestation of cardiomyopathy. In a recent prospective study,[34] a similar influenza-like syndrome occurring shortly before the initial symptoms of cardiomyopathy was reported in 10 of 18 patients. A relation between viral infection and cardiomyopathy is suggested by several other studies,[34–42] but complete evidence is still lacking.

Other contributing factors: In some of our patients in this study, possible contributing factors were rheumatic fever, puerperium and a family history of cardiomyopathy. The frequency of a convincing history of rheumatic fever (8 percent of our patients) was too high to be merely coincidental; it is not certain whether these patients were affected by chronic or recurrent rheumatic myocarditis that led to the dilated cardiomyopathy or whether the early rheumatic process had altered the myocardial immunologic response and thus predisposed the patients to cardiomyopathy. The development of dilated cardiomyopathy during pregnancy or in the puerperium has been noted previously[11,43–46] but was present in only three of our patients. A family history of idiopathic dilated cardiomyopathy is rare[11,47,48] and was present in only 2 of our 104 patients. Although a positive family history of cardiomyopathy and the puerperium may be factors in the genesis of cardiomyopathy, the intrinsic mechanism remains unknown.

Implications: It appears reasonable to consider dilated cardiomyopathy the final common pathway of many different disorders. Future investigations will probably focus on patients identified at an earlier stage of the disease. At a minimum, these studies should include (1) prospective and systematic observations in various populations of the risk factors and the natural history of the disease (such as defined in this retrospective study), and (2) serial myocardial biopsy for the assessment of histologic and ultrastructural changes, as well as cell and serologic identification of possible ongoing infectious and immunologic processes. Such studies, aiming for a better understanding of the underlying cause or causes during the early stages of the disease, may reveal meaningful methods of prophylaxis and treatment.[49–52]

Acknowledgment

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Prognosis in Hypertrophic Cardiomyopathy: Role of Age and Clinical, Electrocardiographic and Hemodynamic Features

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Retrospective analysis of the clinical course of 254 patients with hypertrophic cardiomyopathy, followed up for 1 to 23 years (mean 6), disclosed that 58 had died, 32 of them suddenly. The 196 survivors were compared with the 32 patients who died suddenly and with the 38 who died suddenly or with heart failure. The combination of young age (14 years or less), syncope at diagnosis, severe dyspnea at last follow-up and a family history of hypertrophic cardiomyopathy and sudden death best predicted sudden death (false negative rate 30 percent, false positive rate 27 percent). A "malignant" family history was associated with poor prognosis, particularly in the younger patients; a family history of hypertrophic cardiomyopathy without sudden death was more frequent in the survivors (12 percent) than in the dead (5 percent). Patients who had a diagnosis in childhood were usually asymptomatic, had an unfavorable family history and a 5.9 percent annual mortality rate. In those aged 15 to 45 years at diagnosis, there was a 2.5 percent annual mortality rate and syncope was the only prognostic feature. Among those diagnosed between age 45 and 60 years, dyspnea and exertional chest pain were more common in the patients who died, and the annual mortality rate was 2.6 percent. Poor prognosis was better predicted by the history at the time of diagnosis and by changes in symptoms during follow-up than by any electrocardiographic or hemodynamic measurement.

Hypertrophic cardiomyopathy, first recognized clinically by Brock,[1] was characterized by Goodwin et al.[2] and Braunwald et al.[3] At the Royal Postgraduate Medical School sudden death was the most common mode of death.[4] The purpose of this study is to relate specific clinical, electrocardiographic and hemodynamic features to prognosis and to examine the evidence that a family history of the disease,[4] blackouts[5] and diagnosis in childhood[6] were of ill omen.

Methods

Study patients: Retrospective analysis to assess the prognostic value of clinical, electrocardiographic and hemodynamic features at diagnosis and clinical features at last follow-up was performed on 254 patients with hypertrophic cardiomyopathy who were diagnosed and followed up at the Royal Postgraduate Medical School. Although noncardiac and cardiac surgical deaths are discussed, the comparative analysis included only those patients who died with heart failure or suddenly. The clinical information was always taken from observations by one of us.

The diagnosis of hypertrophic cardiomyopathy was based on typical clinical features,[2,3] M mode echocardiography[7] and left ventricular angiography.[8] In 228 patients the diagnosis was established by left ventricular angiography. Twenty-six patients were diagnosed noninvasively: Ten patients were first degree relatives of propositi and had clinical, electrocardiographic or echocardiographic features consistent with hypertrophic cardiomyopathy, whereas 16 patients had the typical clinical and echocardiographic features of hypertrophic cardiomyopathy and a left ventricular outflow tract gradient.[3,7,9] We do not believe that hypertrophic cardiomyopathy without a gradient can always be clinically or

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echocardiographically differentiated from secondary forms of left ventricular hypertrophy, and therefore we performed angiography in all such patients.[10]

Mode of diagnosis: Since the diagnostic use of M mode echocardiography became widely available in the early 1970s, the bias of selection of patients may have changed; we therefore examined why investigations were performed in our patients. Diagnosis was made between 1957 and 1972 in 140 patients and since 1972 in 114 patients. Two hundred forty-one of the patients were studied for evaluation of symptoms, the presence of a systolic murmur, an abnormal apex beat or an abnormal electrocardiogram. In 10 patients diagnosis was made during the evaluation of first degree relatives of propositi. An additional 26 living and 32 dead family members of propositi have or had definite or probable hypertrophic cardiomyopathy; they are not, however, included in the analysis because of incomplete diagnostic or follow-up information. In three patients diagnosis was made after investigation for clinical features suggestive of mitral stenosis[11]; in these patients a clinically unsuspected diagnosis of hypertrophic cardiomyopathy was made by echocardiography. There were, however, no other patients in whom initial referral or diagnosis of hypertrophic cardiomyopathy was based solely on the echocardiogram. Our evaluation of M mode echocardiography in prognosis was previously published.[12]

Follow-up: Sixty-nine percent of the patients were seen on a follow-up examination within 2 years before the study; 16 patients were excluded because they had no follow-up for at least 5 years before the analysis. One hundred fifty-two patients were male and 102 were female. The age at diagnosis was 1 to 66 years (mean 34). The length of the follow-up period was 1 to 23 years (mean 6). We were unable to obtain retrospective information on the influence of beta adrenergic blocking therapy on prognosis because our policy had been to treat all patients with hypertrophic cardiomyopathy with beta blocking agents.

The electrocardiogram recorded at the time of diagnosis was evaluated for rhythm disturbances, particularly atrial fibrillation; conduction disease, including the P-R interval, the Q-T interval corrected for heart rate (Q-Tc = Q-T/R-R interval), left axis deviation (mean frontal QRS axis −30° to −150°) and bundle branch block[13]; left or right atrial enlargement[13]; and voltage criteria of left ventricular hypertrophy.[14]

Left heart catheterization had been performed in 228 patients, and 198 of the patients had also undergone right-sided hemodynamic study. Patients were considered to have a left ventricular outflow tract gradient if the pressure gradient measured under basal conditions or with provocation (at first with isoproterenol infusion, later with amyl nitrate inhalation or the Valsalva maneuver) was 20 mm Hg or greater.

Analysis of data: A stepwise discriminant analysis was performed to compare the patients who died with heart failure or suddenly, or both groups, with the survivors; 24 clinical, electrocardiographic and hemodynamic features were used as independent variables. The chi-square test or, when appropriate, Fisher's exact test was used for qualitative comparison and the *t* test was used for quantitative comparison of clinical, electrocardiographic and hemodynamic features of the survivors and the dead. Cumulative survival rates were derived from life table calculations.[15]

Results

Age and family history: Fifty-eight patients (23 percent) had died, 6 (11 percent) from cardiac failure and 32 (55 percent) suddenly. All 32 sudden deaths were unexpected; 24 were witnessed and were instantaneous; in the remaining 8 cases, the patient was found dead. In the remaining 20 patients, death was due to cerebral embolus (one patient, 2 percent), infective endocarditis (two patients, 3 percent), cardiac surgery (nine patients, 15 percent), noncardiac causes (seven patients, 12 percent) and accident during electrophysiologic study (one patient, 2 percent). The mean age at diagnosis was 30 years (range 3 to 66), which was significantly lower than that of the 196 survivors ($p < 0.03$). Eleven of the dead patients were aged 14 years or younger at the time of diagnosis (Table I). The duration of follow-up was 5.7 ± 5.3 years in the survivors and 6.2 ± 4.8 years in the dead (Table I). The age at death was 7 to 67 years (mean 37); 12 (31 percent) of the dead patients were aged 30 years or younger at the time of death. The six patients who died with heart failure were aged 14 to 66 years (mean 38) when they died.

Nine (24 percent) of 38 patients who died suddenly or with cardiac failure had a positive family history of hypertrophic cardiomyopathy and unexplained sudden death compared with 23 (12 percent) of the survivors ($p = 0.06$). In childhood an unfavorable family history was associated with sudden death ($p < 0.01$): 4 of the 11 patients who died had at least one, and three had more than one, first degree relative who died from hypertrophic cardiomyopathy. Although 29 percent of the patients who died had a first degree relative with hypertrophic cardiomyopathy, so did 24 percent of the survivors (Table II).

Symptoms: The symptoms at the time of diagnosis in the patients who are dead and the survivors are compared in Table III. Severe dyspnea (New York

TABLE I

Age at Diagnosis in Relation to Duration of Follow-up and Prognosis

	Age at Diagnosis (yr)									
	≤14		15–30		31–45		46–60		>60	
	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive
Patients										
n	11	16	9	58	8	61	9	55	1	6
%	41	59	13	87	12	88	14	86	14	86
Duration of follow-up (yr)	4.7	9.0	7.2	6.4	6.8	5.3	7.1	4.8	1.0	1.5

TABLE II

Family History in Hypertrophic Cardiomyopathy: Comparison of 196 Survivors and 38 Dead*

	Family History							
	None		Hypertrophic Cardiomyopathy		Sudden Death		Hypertrophic Cardiomyopathy and Sudden Death	
	n	%	n	%	n	%	n	%
Alive	133	67	22	12	18	9	23	12
Dead	20	53	2	5	7	18†	9‖	24‡,§

* Thirty-two died suddenly and six died with cardiac failure. † $p < 0.025$. ‡ $p = 0.06$ for sudden death and hypertrophic cardiomyopathy. § $p < 0.05$ for sudden death with or without documented hypertrophic cardiomyopathy. ‖ Six of these nine patients had multiple sudden deaths from hypertrophic cardiomyopathy in their families.

TABLE III

Clinical Comparison of 196 Survivors and 38 Patients Who Died*

	Symptoms at Time of Diagnosis (% of patients)					
				Dyspnea (NYHA class)		
	Dizziness	Syncope	Exertional Chest Pain	I	II	III and IV
Alive	25	17	54	41	50	9
Dead	29	32 ($p < 0.05$)	48	37	50	13

* Thirty-two died suddenly and six died with heart failure.
NYHA = New York Heart Association.

Heart Association functional class III or IV) was uncommon and did not predict poor prognosis. Although more dead patients had dizziness, only syncope ($p < 0.05$) was associated with death.

Electrocardiography: Table IV summarizes the comparison of the electrocardiogram at the time of diagnosis in the living patients and those who had died: 4 percent of the survivors and 11 percent of the dead had atrial fibrillation (this difference was not significant), and the mean P-R interval and the mean corrected Q-T interval were almost identical in both groups. Overt preexcitation was present in five patients (2 percent); another patient with concealed Wolff-Parkinson-White syndrome died during electrophysiologic study when atrial pacing initiated ventricular tachycardia that degenerated to ventricular fibrillation.[16] Although complete bundle branch block was rare, incomplete bundle branch block was present in 20 (10 percent) of the survivors and 9 (24 percent) of the dead and was associated with a worse prognosis ($p < 0.04$). The voltage criteria for left ventricular hypertrophy were present in 67 percent of the survivors and 69 percent of the deceased, and the difference in mean voltage amplitude in the two groups was not significant.

Hemodynamics: Table V presents a hemodynamic comparison of the living and dead patients using data from the original diagnostic catheterization study. The mean right atrial, pulmonary capillary wedge and left ventricular end-diastolic pressures were similarly elevated in both groups. Sixty-six percent of the patients who died and 63 percent of the survivors had a resting or provocable left ventricular outflow tract gradient, and neither the presence nor the absence of a gradient predicted subsequent mortality.

The prognostic significance of clinical, electrocardiographic and hemodynamic features in relation to the age at diagnosis is assessed in Tables VI to VIII. No hemodynamic or electrocardiographic feature was associated with death; however, syncope in patients less than 45 years of age indicated a poor prognosis ($p < 0.01$). Exertional chest pain and dyspnea were more common in the older patients who died (more than 45 years) than in the older survivors.

Symptoms at last follow-up study: Table IX compares the clinical features at the last follow-up exami-

TABLE IV

Electrocardiographic Comparison of 196 Survivors and 38 Patients Who Died

	Electrocardiographic Findings at Time of Diagnosis							
	AF (%)	Atrial Enlargement (%)	$\overline{P\text{-}R}$ (s)	$\overline{Q\text{-}Tc}$ (s)	BBB (%)	LAD (%)	R in aVL (mean) (mm)	S in V_1 + R in V_5 (mm)
Alive	4	47	0.17	0.43	3	31	11.2 ± 8.8	40.0 ± 18.0
Dead	11	42	0.16	0.43	3	22	10.9 ± 7.1	39.7 ± 18.6

AF = atrial fibrillation; atrial enlargement = left atrial or right atrial enlargement, or both; BBB = bundle branch block; LAD = left axis deviation P-R = mean P-R interval; Q-Tc = mean Q-T interval corrected for heart rate; R in aVL = mean R wave amplitude in lead aVL; S in V_1 + R in V_5 = mean sum of the S wave amplitude in lead V_1 and the R wave amplitude in lead V_5.

nation in the survivors and the patients who died. The incidence of symptoms at follow-up was lower than that at diagnosis; although more of the dead patients had syncope and dizziness, only severe dyspnea (New York Heart Association class III or IV) ($p < 0.05$) was associated with a poor prognosis.

Predictors of sudden death: Discriminant analysis disclosed that the combination of the following features best predicted sudden death: young age (14 years or less) and syncope at diagnosis, a positive family history of hypertrophic cardiomyopathy and sudden death, and severe dyspnea (functional class III or IV) at last follow-up examination. Sixteen of 23 dead patients (false negative rate 30 percent) and 111 of 163 survivors (false positive rate 27 percent) were correctly identified. When the deaths from heart failure (six patients) were included with the sudden deaths, the combination of young age (14 years or less), congestive heart failure and syncope at diagnosis, severe dyspnea at last follow-up examination, conduction defects (incomplete or complete bundle branch block) and left or right atrial enlargement on electrocardiography best predicted mortality. The outcome in 21 of the 30 dead patients (false negative rate 30 percent) and 133 of the 160 survivors (false positive rate 17 percent) was correctly predicted by the analysis.

Role of surgery: The initial treatment at the time of diagnosis and the current therapy are summarized in Table X. Digoxin was used to treat patients with heart failure and atrial fibrillation. Apart from verapamil and beta adrenergic blocking agents, only 7 percent of the 254 patients ever received antiarrhythmic drugs. Thirty-three patients had undergone myotomy-myomectomy or mitral valve replacement, or both (27 patients before 1975), and 9 of these patients died perioperatively. The annual mortality rate in the surgical survivors was 1.8 percent. Six of the 24 patients who survived the operation subsequently died 1 to 20 years (mean 6) after the operation (1 from documented ventricular fibrillation, 3 suddenly, 1 with heart failure and another in an accident). Although a resting or provo-

TABLE V

Hemodynamic Comparison of 196 Survivors and 38 Patients Who Died

	Hemodynamic Measurements at Time of Diagnosis					
				LVOT Gradient (%)		
	RA (mm Hg)	PCW (mm Hg)	LVEDP (mm Hg)	Resting	Provocable	None
Alive	9.5 ± 4.3	15.6 ± 6.7	18.5 ± 11.0	39	24	37
Dead	10.0 ± 5.8	14.7 ± 6.7	17.8 ± 9.7	47	19	34

LVEDP = mean left ventricular end-diastolic pressure; LVOT = left ventricular outflow tract; PCW = mean pulmonary capillary wedge pressure; RA = mean right atrial pressure.

TABLE VI

Relation of Age and Clinical Features at Diagnosis to Prognosis

	Age at Diagnosis (yr)									
	≤14		15–30		31–45		46–60		>60	
	Dead (n = 11)	Alive (n = 16)	Dead (n = 9)	Alive (n = 58)	Dead (n = 8)	Alive (n = 61)	Dead (n = 9)	Alive (n = 55)	Dead (n = 1)	Alive (n = 6)
Syncope*	4	3	2	13	4	8	1	8	0	1
Exertional chest pain	2	2	2	26	5	26	6	35	0	3
Dyspnea†										
Class II	4	5	5	27	3	33	7	29	0	4
Classes III and IV	0	0	0	6	4	3	1	9	0	0

* Syncope in patients less than 45 years of age was associated with death ($p < 0.01$). † New York Heart Association classification.

TABLE VII

Relation of Age and Electrocardiographic Features at Diagnosis to Prognosis

	Age at Diagnosis (yr)									
	≤14		15–30		31–45		45–60		>60	
	Dead (n = 11)	Alive (n = 16)	Dead (n = 9)	Alive (n = 58)	Dead (n = 8)	Alive (n = 61)	Dead (n = 9)	Alive (n = 55)	Dead (n = 1)	Alive (n = 6)
Bundle branch block	1	0	0	1	0	2	0	2	0	0
Left axis deviation	0	5	2	16	4	17	1	19	1	2
Atrial enlargement	3	7	4	25	3	23	3	26	0	2
R in aVL >12 mm	5	3	1	26	1	18	5	27	1	1
S in V_1 + R in V_5 >35 mm	6	9	4	34	0	30	6	27	1	3

Abbreviations as in Table IV.

TABLE VIII

Relation of Age and Hemodynamic Features at Diagnosis to Prognosis*

	Age at Diagnosis (yr)									
	≤14		15–30		31–45		46–60		>60	
	Dead (n = 11)	Alive (n = 14)	Dead (n = 8)	Alive (n = 57)	Dead (n = 7)	Alive (n = 61)	Dead (n = 9)	Alive (n = 55)	Dead (n = 1)	Alive (n = 6)
LVOT gradient										
Resting	4	8	4	25	4	17	5	21	NS	3
Provocable	1	1	2	7	1	21	2	16	NS	2
None	6	5	2	25	2	23	2	18	NS	1
Mean pressure (mm Hg)										
PCW	14	11	11	14	15	16	20	17	NS	18
LVEDP	16	14	16	17	17	19	22	18	NS	23

* Five patients who did not undergo hemodynamic investigation are excluded.
LVEDP = left ventricular end-diastolic pressure; LVOT = left ventricular outflow tract; NS = not studied; PCW = pulmonary capillary wedge pressure.

TABLE IX

Clinical Comparison of 196 Survivors and 38 Nonsurvivors at Last Follow-up

	At Last Follow-Up (% of patients)							
	New Atrial Fibrillation	Palpitation	Dizziness	Syncope	Exertional Chest Pain	Dyspnea (NYHA class)		
						I	II	III and IV
Alive	7	33	19	8	36	53	39	8
Dead	3	24	26	15	36	41	38	21
							(p <0.05)	

NYHA = New York Heart Association.

cable gradient of at least 30 mm Hg was an essential requirement for operation in all patients, the symptomatic indications for operation have varied. Before 1970 the preoperative symptom status of the surgical patients was similar to that of the medical patients. However, with improved symptomatic treatment in the past 10 years, proportionately fewer patients have been operated on and these have been severely symptomatic with poor response to medical therapy.

Discussion

Sudden death in hypertrophic cardiomyopathy: Our results confirm the impression that sudden death is the most common mode of death in patients with hypertrophic cardiomyopathy.[17] The patients who died were significantly younger at the time of diagnosis than the survivors, and 12 were aged 30 years or younger when they died. The annual mortality rate in the pediatric age group was 5.9 percent (Fig. 1). This is consistent with the findings in a retrospective study in which 18 of 26 patients who died suddenly were aged 20 years or younger and with the findings of a high annual mortality rate (4 percent) in children with hypertrophic cardiomyopathy.[18] Compared with the older patients (Table VI) children have a greater incidence of syncope; however, they are otherwise less symptomatic. The children who died were clinically and electrocardiographically similar to the survivors (Tables VI and VII); their mean filling pressures were similar, and fewer patients who died had a left ventricular outflow tract gradient (Table VIII). Diagnosis in childhood was also associated with a family history of hypertrophic cardiomyopathy and sudden death ($p < 0.01$). Maron et al.[19] described a subgroup of families with malignant hypertrophic cardiomyopathy in which the incidence of premature death was unusually high. In our study 4 of the 11 dead patients whose diagnosis had been made in childhood had at least one first degree relative who died from hypertrophic cardiomyopathy, and 3 of the 4 had more than one relative who had died from hypertrophic cardiomyopathy.

TABLE X

Medical Treatment of 254 Patients With Hypertrophic Cardiomyopathy

Drug	At Diagnosis (%)	At Last Follow-Up (%)
Digoxin*	11	16
Diuretic drug	13	27
Beta blocking agent	67	68
Verapamil	2	4
Antiarrhythmic agent	5	5

* Digoxin was used to treat heart failure and to slow atrioventricular conduction in patients with atrial fibrillation.

Role of family history: A family history of sudden death with or without documented hypertrophic cardiomyopathy was associated with a poor prognosis ($p < 0.05$), despite the bias of patient selection. This did not take into account 32 dead members of "malignant" families who probably had hypertrophic cardiomyopathy but in whom diagnostic or follow-up documentation was inadequate. Twenty-five percent of the patients who died had a positive family history of hypertrophic cardiomyopathy and sudden death, and six of these nine patients who died had multiple sudden deaths in their families. Malignant hypertrophic cardiomyopathy is characterized by sudden death in young asymptomatic patients.[19] In contrast to these "malignant" families were "benign" families with affected members but no sudden deaths; only 2 of 24 propositi of such families died suddenly or in heart failure. Patients with a family history of hypertrophic cardiomyopathy without sudden death had a prognosis similar to that in patients with no family history of hypertrophic cardiomyopathy.

Effect of medical treatment: From the data available we cannot assess the effect of medical treatment, particularly of beta adrenergic blocking drugs. In a prospective nonrandomized study Frank et al.[20] administered "complete" beta receptor blocking doses of propranolol (average dose 462 mg/day) and found improvement in symptoms and no mortality in 22 patients followed up 2 to 8 years (mean 5); in contrast, 4 of 10 control patients died suddenly. Although beta-adrenergic blocking drugs improve symptoms, the effect on prognosis is uncertain and requires further study.

Recently, Rosing et al.[21] reported relief of symptoms and improved exercise capacity in patients with hypertrophic cardiomyopathy treated with the calcium antagonist verapamil. These results are consistent with reports of symptomatic improvement, reduction in heart size (assessed radiographically) and reduced QRS amplitude in the electrocardiogram after large dose (480 to 720 mg/day) long-term treatment with verapamil.[22] Long-term prospective randomized studies of verapamil treatment in hypertrophic cardiomyopathy are needed to assess the effect on prognosis.

Effect of surgical treatment: Although the surgical mortality rate was high, the small number of patients, the changing bias of patient selection and use of different surgical techniques make it difficult to assess the effect of surgical treatment on prognosis. However, the subsequent annual mortality rate in the surgical survivors was 1.8 percent, similar to that in the series with the largest number of surgical survivors (1.8 percent),[23] and less than the annual mortality rate in the medically treated patients (3.5 percent). Nevertheless, because of the high overall operative mortality rate (approximately 27 percent), the total 6 year mortality rate for surgically treated patients exceeded that of medically treated patients.

Predictive importance of the clinical features: A poor prognosis was better predicted by the patient's history than by any electrocardiographic or hemodynamic measurement. At the time of diagnosis older patients were more symptomatic (Table VIII) but

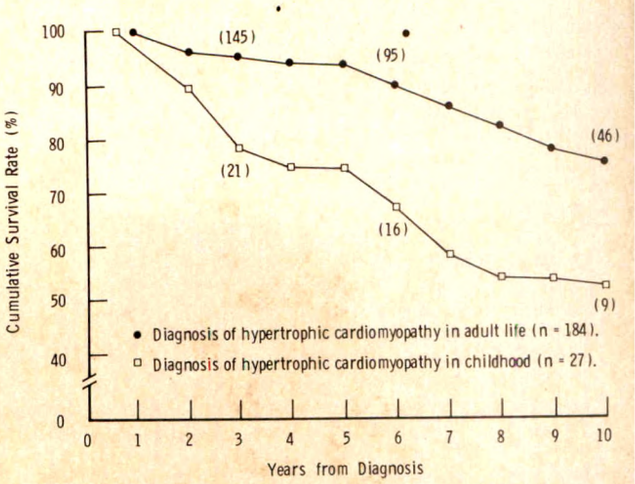

FIGURE 1. Cumulative survival curve from the year of diagnosis for 211 medically treated patients. The probability of death = the total number of deaths for the year divided by the adjusted number at risk, minus the number of deaths due to other causes.[15]

younger patients had a worse prognosis (Fig. 1). The discriminant analysis for the prediction of sudden death included clinical features of severe functional impairment as well as young age and unfavorable family history. However, in the young patients, sudden death was clearly unrelated to severe functional limitation, elevated filling pressure or the presence of a left ventricular outflow tract gradient (Tables VI to VIII). One may speculate that the mechanism of death may be accelerated by worsening hemodynamic state in the older patients but that the underlying mechanism is unlikely to be hemodynamic in the majority of patients; 12 (32 percent) of the 38 dead patients were aged 30 years or younger and 69 percent were in functional class I. Syncope was the only clinical feature associated with sudden death, particularly in patients younger than 45 years ($p < 0.01$) (Table VI).

Mechanisms of sudden death: It is unreasonable to assume that the mechanism of sudden death is the same in all patients with hypertrophic cardiomyopathy; isolated reports of cardiac asystole,[5] massive myocardial infarction[24] and rapid atrioventricular conduction through an accessory pathway degenerating to ventricular fibrillation[16] have been documented as antecedent events. Primary hemodynamic mechanisms, with increased left ventricular outflow tract gradient or tachycardia with acute decrease in stroke volume, have also been proposed.[25] Although it remains unproved, we suspect that ventricular arrhythmia is the antecedent event in most sudden deaths in patients with hypertrophic cardiomyopathy. The large incidence of serious ventricular arrhythmia is well recognized,[26–28] and in our series 55 percent of the deaths were sudden and were associated with a previous history of syncope. Traditional treatment with beta adrenergic blocking drugs[27,28] and the newer treatment with verapamil[29] are ineffective against ventricular arrhythmias in hypertrophic cardiomyopathy. The high (50 percent) incidence rate[26,27] of serious ventricular arrhythmia in

hypertrophic cardiomyopathy was not recognized before the development of ambulatory electrocardiographic monitoring, and only 7 percent of the 254 patients received specific antiarrhythmic drugs other than beta blocking agents or verapamil. Because the detection and effective treatment of arrhythmia may improve prognosis in this condition, we are investigating the value of amiodarone and similar antiarrhythmic agents.

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Comparison of Coronary Arteriographic Findings During Angina Pectoris Associated With S-T Elevation or Depression

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Coronary arteriographic findings during an attack of angina pectoris associated with S-T segment elevation and angina associated with S-T depression were compared in 54 patients. Thirty-eight attacks with S-T segment elevation included 2 that were spontaneous, 6 induced by methacholine, 4 by epinephrine with or without propranolol, 9 by arm exercise, 5 by hyperventilation with or without Tris-buffer infusion and 12 by ergonovine maleate. Twenty-nine of the 38 attacks were associated with total occlusion, 8 with subtotal occlusion and 1 with diffuse narrowing of a major coronary artery caused by spasm.

Twenty-six attacks with S-T segment depression included 3 induced by methacholine, 13 by arm exercise, 3 by hyperventilation with or without Tris-buffer infusion and 7 by ergonovine maleate. Eight of the 26 attacks were associated with subtotal occlusion and 9 with diffuse narrowing of a major coronary artery caused by spasm; 3 attacks were associated with total occlusion of a major coronary artery well supplied with collateral vessels and 2 with total occlusion of a small coronary branch caused by spasm. Four attacks were associated not with spasm but with fixed subtotal occlusion of a major coronary artery (3 attacks) or total occlusion of a major coronary artery receiving collateral vessels (1 attack).

Only 2 of the 31 patients with S-T segment elevation had collateral vessels compared with 8 of the 16 patients with S-T segment depression ($p < 0.001$). It is concluded that angina pectoris associated with S-T segment elevation usually indicates more severe myocardial ischemia than angina associated with S-T segment depression.

S-T segment displacement in the electrocardiogram is one of the most useful signs of acute myocardial ischemia, but the difference between angina pectoris associated with S-T segment elevation and that associated with S-T depression has not been fully elucidated.[1–5] Experimental studies[2,6–8] suggest that S-T segment elevation is associated with more severe ischemia than is S-T depression, the former representing transmural ischemia and the latter subendocardial ischemia.[9–11] We have reported coronary arteriographic findings during angina associated with S-T elevation and during angina associated with S-T depression. In this study, we reviewed and compared the coronary arteriographic findings during angina associated with S-T segment elevation and depression.

Methods

Study patients: We were able to perform coronary arteriography during 64 attacks of angina pectoris (38 associated with S-T segment elevation and 26 with S-T segment depression) in 54 patients. The patients' age and sex, the electrocardiographic findings during angina, coronary arteriographic findings after nitroglycerin administration and in the absence of angina and during angina are shown in Table I. Thirty-one patients (Cases 1 to 31) had recurrent angina associated with S-T segment elevation occurring spontaneously and 17 of the 31 also had exertional angina on occasion. Seven patients (Cases 32 to 38) had spontaneous angina associated with either S-T segment elevation or S-T segment depression in the same leads and four of the seven also had exertional angina

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on occasion. Sixteen patients (Cases 39 to 54) had exertional angina associated with S-T segment depression and eight of them also had spontaneous angina. Patients with myocardial infarction or heart failure were excluded from the study.

Electrocardiography: Standard 12 lead electrocardiograms were taken repeatedly during angina and transient S-T segment elevation of more than 2.0 mm or transient S-T segment depression of more than 1.0 mm from baseline was documented in all patients. S-T segment elevation with reciprocal S-T segment depression in opposing leads was classified as S-T segment elevation.

Methods of provoking angina: Details of the methods of provoking angina have previously been reported.[9–13] These methods have been confirmed to be safe in experienced hands

TABLE I

Patients With Arteriography During Anginal Attack

Case	Age (yr) & Sex	ECG Changes During Attack	Coronary Arteriogram After Nitroglycerin		
			% Stenosis	Collateral Vessels	Spasm and % Stenosis
1	66M	S-T ↑ in II, III, aVF	90% S2, 75% S3, 50% S11	No	Spontaneous: 100% S2
2	63M	S-T ↑ in II, III, aVF	75% S7	No	Spontaneous: 99% S1 Methacholine-induced: 100% S1
3	58M	S-T ↑ in II, III, aVF	Normal	No	Methacholine-induced: 100% S1
4	48M	S-T ↑ in II, III, aVF	Normal	No	Methacholine-induced: 100% S1
5	59M	S-T ↑ in V_{1-4}	90% S6	No	Methacholine-induced: 100% S6
6	41M	S-T ↑ in V_{1-4}	25% S6	No	(1) Methacholine-induced: 100% S6; (2) Epinephrine-induced: 99% S6
7	62M	S-T ↑ in II, III, aVF	50% S2	No	Epinephrine-induced: 100% S2
8	48M	S-T ↑ in II, III, aVF	Normal	No	Epinephrine-induced: 99% S1
9	53M	S-T ↑ in II, III, aVF	90% S2, 25% S6	No	Epinephrine-induced: 99% S2
10	56M	S-T ↑ in V_{1-4}	25% S1, 25% S6	No	Exercise-induced: 100% S6
11	57M	S-T ↑ in V_{2-4}	90% S7, 50% S10	No	(1) Exercise-induced: (2) Hyperventilation-induced: 100% S7
12	47F	S-T ↑ in V_{2-4}	75% S7	No	(1) Exercise-induced: (2) Hyperventilation-induced: 100% S7
13	57M	S-T ↑ in V_{1-4}	90% S7	No	Exercise-induced: 100% S7
14	45F	S-T ↑ in II, III, aVF	25% S3, 25% S6	No	Exercise-induced: 100% S3
15	56M	S-T ↑ in II, III, aVF	75% S4	No	Exercise-induced: 100% S2
16	57M	S-T ↑ in V_{1-5}	90% S6	No	(1) Exercise-induced: (2) Ergonovine-induced: 99% S6
17	64M	S-T ↑ in II, III, aVF	75% S3, 25% S6	No	Exercise-induced: 100% S3

TABLE I. (continued)

Case	Age (yr) & Sex	ECG Changes During Attack	Coronary Arteriogram After Nitroglycerin		
			% Stenosis	Collateral Vessels	Spasm and % Stenosis
18	62M	S-T ↑ in V_{2-4}	25% S2, 25% S4 50% S7, 25% S9	No	Hyperventilation-induced: 100% S7
19	61F	S-T ↑ in II, III, aVF	90% S1, 50% S2 50% S7, 75% S12	Yes	Hyperventilation-induced: 99% S2
20	48F	S-T ↑ in V_{2-4}	75% S7, 50% S9	No	Hyperventilation-induced: 100% S7
21	63M	S-T ↑ in V_{1-5}	90% S6, 90% S11 75% S12	No	Ergonovine-induced: 100% S6
22	59M	S-T ↑ in II, III, aVF	Normal	No	Ergonovine-induced: 99% S1
23	49M	S-T ↑ in V_{1-4}	50% S3, 90% S6 75% S9, 25% S14	Yes	Ergonovine-induced: 100% S6
24	63M	S-T ↑ in II, III, aVF	25% S7	No	Ergonovine-induced: 100% S1
25	66M	S-T ↑ in V_{2-4}	90% S7	No	Ergonovine-induced: 100% S7
26	55M	S-T ↑ in V_{2-4}	50% S7	No	Ergonovine-induced: 99% S7
27	52M	S-T ↑ in II, III, aVF, V_{5-6}	25% S6	No	Ergonovine-induced: 100% S11
28	59F	S-T ↑ in V_{2-4}	75% S7, 75% S8	No	Ergonovine-induced: diffuse narrowing (S6–S10)
29	59M	S-T ↑ in V_{2-4}	90% S6	No	Ergonovine-induced: 100% S6
30	62M	S-T ↑ in II, III, aVF	90% S2, 75% S3 75% S6, 75% S11	No	Ergonovine-induced: 100% S2
31	65M	S-T ↑ in II, III, aVF	90% S2, 75% S6 50% S11	No	Ergonovine-induced: 100% S2
32	61M	S-T ↑ in V_{1-5} or S-T ↓ in V_{3-5}	25% S2, 75% S6	No	Methacholine-induced: 100% S6 Exercise-induced: 99% S6
33	52M	S-T ↑ in II, III, aVF or S-T ↓ in II, III, aVF	25% S6	No	Exercise-induced: 100% S1 Hyperventilation-induced: diffuse narrowing (S1–S4)
34	54M	S-T ↑ in V_{2-4} or S-T ↓ in V_{3-5}	50% S6	No	Methacholine-induced: 99% S6
35	54M	S-T ↑ in V_{2-4} or S-T ↓ in V_{3-6}	25% S1, 75% S7	No	Exercise-induced: 99% S7
36	48F	S-T ↑ in II, III, aVF, V_{5-6} or S-T ↓ in I, II, III, V_{3-6}	Normal	No	Exercise-induced: diffuse narrowing (S11–S15)

TABLE I (continued)

Case	Age (yr) & Sex	ECG Changes During Attack	Coronary Arteriogram After Nitroglycerin		
			% Stenosis	Collateral Vessels	Spasm and % Stenosis
37	62M	S-T ↑ in V_{1-4} or S-T ↓ in V_{3-5}	90% S6	No	Ergonovine-induced: 99% S6
38	55M	S-T ↑ in V_{2-4} or S-T ↓ in V_{3-6}	50% S7	No	Ergonovine-induced: 99% S7
39	52M	S-T ↓ in in V_{4-5}	25% S2, 25% S6 90% S12	No	Methacholine-induced: 100% S12
40	48M	S-T ↓ in I, II, V_{3-6}	99% S2, 90% S6 75% S11	Yes	(1) Exercise-induced: (2) Hyperventilation-induced: 100% S6
41	42F	S-T ↓ in I, II, V_{3-6}	75% S6	No	(1) Methacholine-induced: (2) Exercise-induced: diffuse narrowing (S6–S10)
42	64M	S-T ↓ in I, II, V_{3-6}	90% S7, 50% S9 50% S12	Yes	Exercise-induced: 99% S7
43	58F	S-T ↓ in I, II, V_{2-6}	25% S1, 25% S2 90% S7, 90% S8	Yes	Exercise-induced: 99% S7
44	63M	S-T ↓ in I, II, V_{4-6}	25% S6	No	Exercise induced: diffuse narrowing (S6–S10)
45	56M	S-T ↓ in I, II, V_{3-6}	75% S13	No	Exercise-induced: 100% S13
46	59F	S-T ↓ in I, II, V_{3-6}	99% S6, 75% S9	Yes	Exercise-induced: diffuse narrowing (S6–S10)
47	55M	S-T ↓ in I, II, V_{2-6}	25% S2, 100% S7 90% S11	Yes	(1) Exercise-induced: (2) Hyperventilation-induced: no spasm
48	58M	S-T ↓ in I, II, V_{3-6}	75% S6, 90% S9 99% S13	No	Exercise-induced: no spasm
49	51M	S-T ↓ in I, II, V_{3-6}	99% S6, 75% S8 90% S12, 50% S2	Yes	Exercise-induced: no spasm
50	33F	S-T ↓ in I, II, V_{4-5}	99% S7	Yes	Ergonovine-induced: no spasm
51	54M	S-T ↓ in I, II, V_{3-6}	25% S1, 75% S6 90% S9	No	Ergonovine-induced: diffuse narrowing (S6–S10)
52	38M	S-T ↓ in I, II, V_{4-6}	90% S6	Yes	Ergonovine-induced: 100% S6
53	64F	S-T ↓ in I, II, V_{4-6}	Normal	No	Ergonovine-induced: diffuse narrowing (S6–S15)
54	55M	S-T ↓ in I, II, V_{4-6}	75% S6	No	Ergonovine-induced: 99% S6

S1 to S15 refer to the segment of the coronary arteries as defined by the American Heart Association Report[14]; S-T ↑ and ST ↓ = S-T segment elevation and depression, respectively.

at our institution. Multiple provocative methods were used because in any one patient one test could be provocative and another not. For example, when arm exercise failed to provoke an attack, ergonovine was successful. Most of the attacks during coronary arteriography were induced in the early morning (from 5:00 a.m. to 8:00 a.m.). Of the 38 attacks associated with S-T segment elevation during coronary arteriography, 2 were spontaneous, 6 were induced by subcutaneous injection of methacholine (10 mg), 4 by subcutaneous injection of epinephrine (0.4 to 0.5 mg) with or without prior oral administration of propranolol (40 to 60 mg), 9 by arm exercise, 5 by hyperventilation with or without Tris-buffer infusion and 12 by intravenous injection of ergonovine maleate (0.05 to 0.2 mg).

Of the 26 attacks associated with S-T segment depression during coronary arteriography, 3 were induced by subcutaneous injection of methacholine (10 mg), 13 by arm exercise, 3 by hyperventilation with or without Tris-buffer infusion and 7 by intravenous injection of ergonovine maleate (0.05 to 0.2 mg).

Coronary arteriography: Coronary arteriography was performed in the morning with the Judkins technique with constant monitoring of the electrocardiogram and blood pressure. Administration of all medications except nitroglycerin had been stopped at least 2 days before the procedure, and use of nitroglycerin had also been stopped at least 2 hours before the procedure. Coronary arteriography was done before, during and after an attack of angina. The angina was relieved promptly by sublingual administration of nitroglycerin, 0.6 mg.

Written informed consent was obtained from each patient.

Results

Coronary arterial spasm: Coronary arteriography demonstrated that spasm of an artery supplying the area of myocardium represented by S-T segment shift in the electrocardiogram appeared during an attack of angina and disappeared with subsidence of the attack after nitroglycerin administration in all 38 attacks associated with S-T segment elevation and in 22 of the 26 attacks associated with S-T depression (Table I). Four attacks with S-T depression (Cases 47 to 50) were not associated with an appreciable coronary arterial spasm.

Degree and location of spasm (Fig. 1): Coronary arteries in the arteriograms were divided into 15 segments according to the classification of the American Heart Association Committee Report.[14] Of the 38 attacks with S-T elevation, 29 were associated with total occlusion, 8 with subtotal occlusion (99 percent of luminal diameter) and 1 with spasm-induced diffuse narrowing (60 to 90 percent of luminal diameter) of a major coronary artery. Total occlusion was generally associated with more severe S-T elevation than was subtotal occlusion or diffuse narrowing.

Thus, the majority (76.3 percent) of the attacks with S-T elevation were associated with total occlusion of a major coronary artery.

Of the 26 attacks of angina associated with S-T depression, 8 were associated with subtotal occlusion and 9 were associated with diffuse narrowing of a major

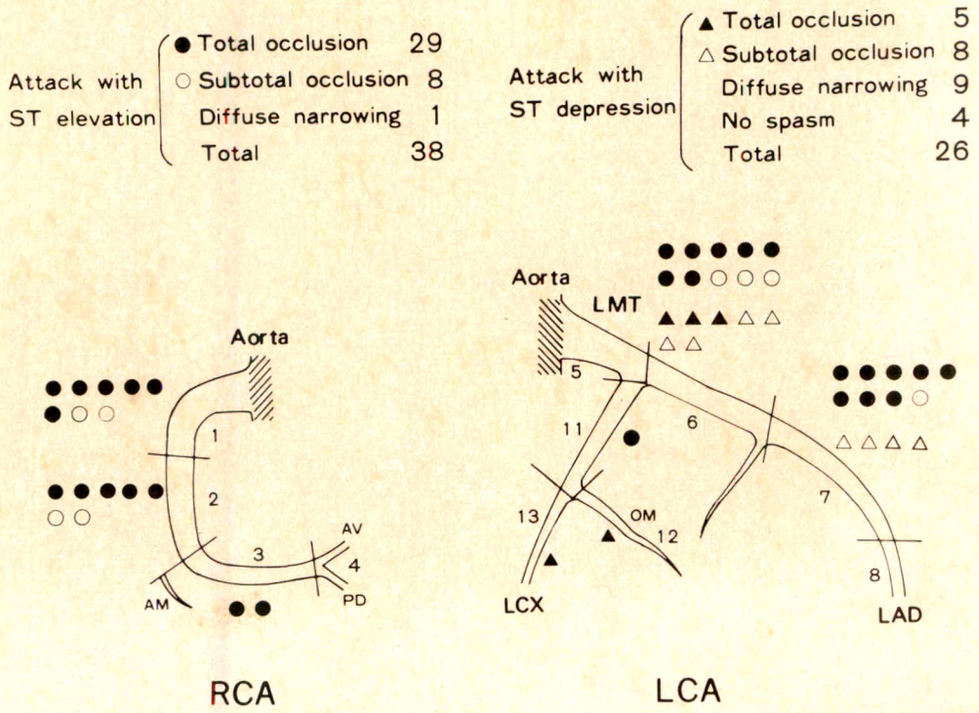

FIGURE 1. Coronary arteriographic findings during acute angina with S-T segment elevation and acute angina with S-T depression. Coronary arteries were divided into 15 segments according to the American Heart Association Committee Report[14] as shown by the number in the diagram of coronary arteries. AM = acute marginal branch; AV = A-V nodal branch; LAD = left anterior descending coronary artery; LCA = left coronary artery; LCX = left circumflex coronary artery; LMT = left main trunk; OM = obtuse marginal branch; PD = posterior descending branch; RCA = right coronary artery.

coronary artery caused by spasm. In two patients (Cases 40 and 52) spasm totally occluded the left anterior descending artery at segment 6 during the attack, but there was a rich supply of collateral vessels to the distal part of this segment in both patients. In one patient (Case 45) spasm totally occluded the poorly developed left circumflex artery at segment 13 during the attack, and in one patient (Case 39) spasm totally occluded the left circumflex artery at segment 12 (obtuse marginal branch). In four patients (Cases 47 to 50), the attacks were associated not with spasm, but with fixed subtotal occlusion of a major coronary artery (Cases 48 to 50) or total occlusion of a major coronary artery receiving collateral vessels (Case 47).

In two patients (Cases 32 and 33) whose attacks were associated with either S-T elevation or S-T depression in the same leads, coronary arteriograms were obtained during both types of attack. In both patients angina with S-T elevation was associated with total spastic occlusion of a major coronary artery (Fig. 2 and 3), whereas angina with S-T depression was associated with either subtotal occlusion (Case 32, Fig. 2) or diffuse narrowing (Case 33, Fig. 3) of the same artery.

Thus, the majority (76.9 percent) of anginal attacks associated with S-T segment depression were accompanied by either subtotal spastic occlusion or diffuse narrowing of a major coronary artery. When the attack with S-T segment depression was associated with total occlusion, the occlusion occurred either in a major coronary artery receiving many collateral vessels to its periphery or in a small branch of a major coronary artery.

Extent of coronary artery disease: Coronary artery disease was defined as fixed arteriographic narrowing greater than 50 percent of luminal diameter. Of the 31 patients with angina associated with S-T segment elevation, 9 had normal coronary arteries and 16 had single, 3 double and 3 triple vessel disease. Of the seven patients with angina associated with either S-T segment elevation or depression in the same leads, 2 had normal coronary arteries and 5 had one vessel disease. Of the 16 patients with angina associated with S-T segment depression, 2 had normal coronary arteries and 9 had single, 4 double and 1 triple vessel disease.

Thus, there was no difference in the extent of coronary artery disease in patients whose angina was asso-

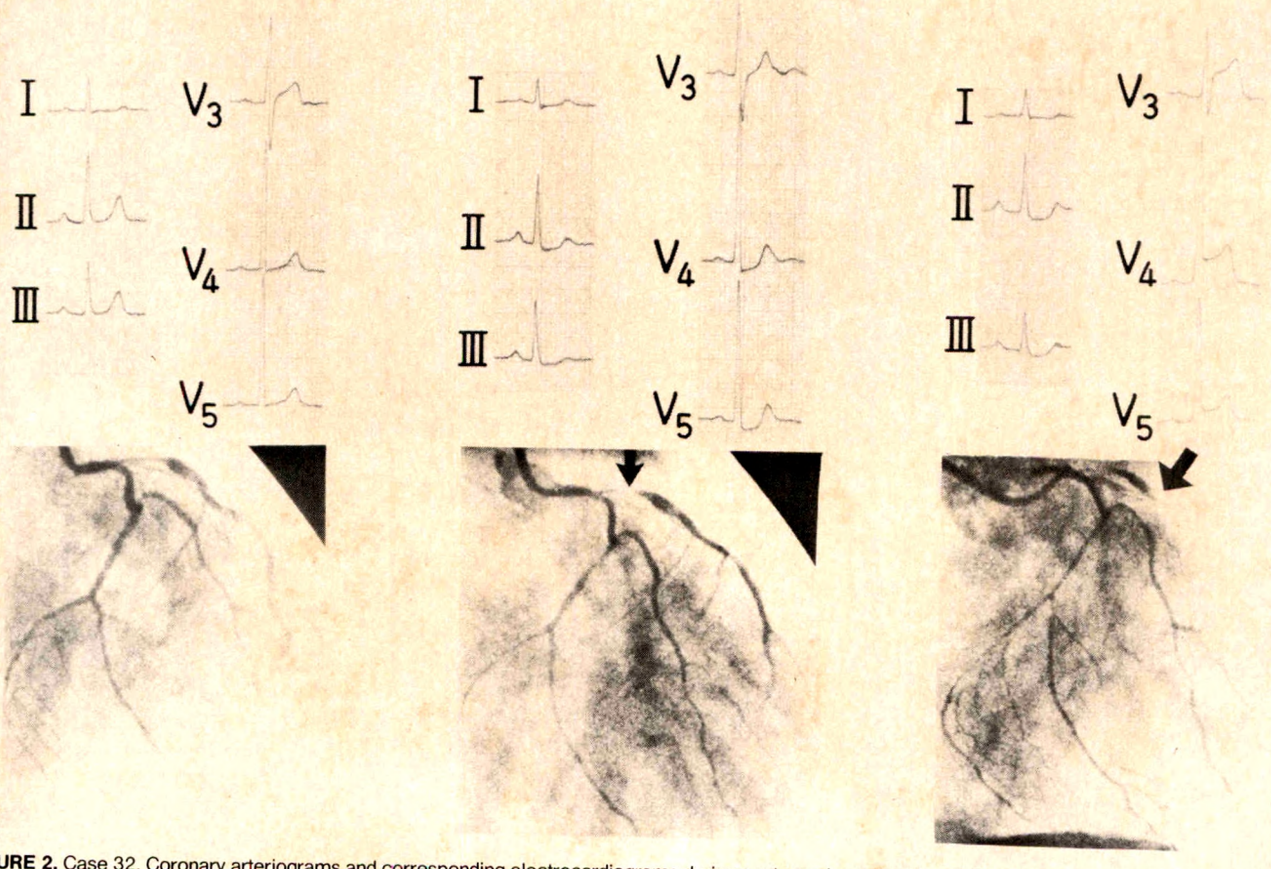

FIGURE 2. Case 32. Coronary arteriograms and corresponding electrocardiograms during acute angina with either S-T segment elevation or depression in the precordial leads. During angina with S-T elevation, spasm totally occluded the left anterior descending coronary artery at segment 6 (**right**). During angina with S-T depression, spasm subtotally occluded the same artery at the same segment (**center**). The **left panel** shows the control coronary arteriogram and electrocardiogram.

ciated with S-T segment elevation or depression. But this finding was probably related to the small number of patients with multivessel disease included in this study.

Collateral circulation: Collateral circulation was present in 2 of the 31 patients with S-T segment elevation and in 8 of the 16 patients with S-T segment depression. This difference was statistically significant ($p < 0.001$). None of the seven patients with either S-T elevation or S-T depression in the same leads had collateral circulation.

Discussion

Angina pectoris is usually associated with either S-T segment elevation or S-T segment depression in the electrocardiogram. Experimental animal studies[2,6–8] suggest that S-T elevation is associated with more severe (transmural) ischemia and S-T depression is associated with less severe (subendocardial) ischemia. Ekmekci et al.[2] demonstrated in the dog that total ligation of a major coronary artery produced S-T elevation in the ischemic area and that S-T depression replaced S-T elevation when the ligation was released or collateral circulation was supplied to the ischemic area. Kato et al.[7] also showed in the dog that S-T elevation was associated with more severe constriction of a major coronary artery than was S-T depression and that total occlusion of a small branch produced S-T depression.

Degree of coronary constriction and myocardial ischemia in angina with S-T elevation versus S-T depression: The results of our study in human beings are in agreement with the data from these animal experiments. Almost all of the acute attacks of angina pectoris with S-T segment elevation were associated with total or subtotal occlusion of a major coronary artery caused by spasm and the degree of S-T elevation paralleled roughly the degree of constriction of the artery. In contrast, angina pectoris with S-T depression during the attack was associated with either less severe spastic constriction (diffuse narrowing or subtotal occlusion) of a major coronary artery or total occlusion of a major coronary artery receiving a rich supply of collateral vessels or total occlusion of a small coronary branch. Moreover, 8 of the 16 patients with S-T depression had collateral vessels compared with only 2 of the 31 patients with S-T elevation.

Thus, it is reasonable to conclude that angina pectoris with S-T segment elevation is usually associated with more severe myocardial ischemia than is angina pectoris with S-T depression, the former representing transmural ischemia and the latter subendocardial ischemia as demonstrated in animal experiments.

Role of coronary spasm: All 38 anginal attacks with S-T segment elevation and 22 of the 26 attacks with S-T depression in our study were associated with coronary arterial spasm. Thus, coronary spasm plays an important role in the production of angina associated with S-T segment elevation as well as, in some cases, that associated with S-T depression. These observations are in agreement with those of Maseri et al.[15,16] Our study also

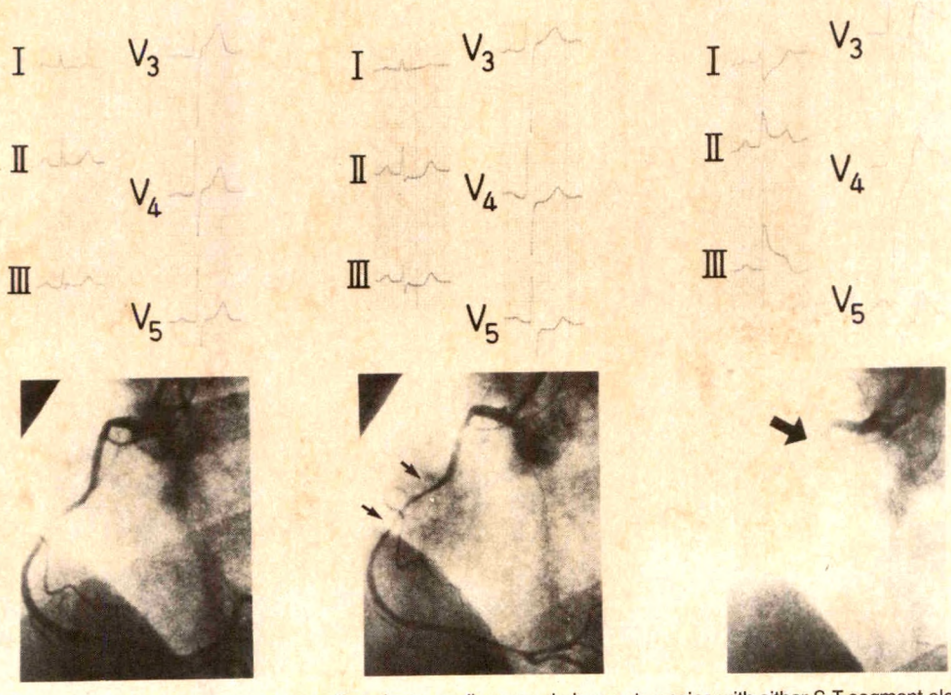

FIGURE 3. Case 33. Coronary arteriograms and corresponding electrocardiograms during acute angina with either S-T segment elevation or depression in the inferior leads. During angina with S-T elevation, spasm totally occluded the right coronary artery at segment 1 (**right**). During angina with S-T depression, diffuse narrowing of the same artery appeared (**center**). The **left panel** shows the control arteriogram and electrocardiogram.

confirms our previous findings[10,11] that coronary arterial spasm can be a cause of some exertional angina.

Implications: Our results do not necessarily support that angina pectoris is almost always caused by coronary arterial spasm. There may be many patients whose anginal episodes are not associated with appreciable spasm. Our observations were limited to a small number of patients whose anginal attacks could be induced in the catheterization laboratory by the methods described, usually in the early morning.

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Coronary Flow Studies in Patients With Left Ventricular Hypertrophy of the Hypertensive Type

Evidence for an Impaired Coronary Vascular Reserve

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Increased myocardial blood flow occurs in ventricular hypertrophy, but flow per 100 grams of myocardium remains normal. The increase in flow may be obtained at the expense of the existing coronary vascular reserve or by an increase in the vascular bed. The coronary vascular reserve was studied by analyzing the hyperemic reaction to selective injection of contrast agent into the coronary arteries in 25 patients: a control group (9 patients) with chest pain syndrome, normal coronary arteries and a normal left ventricle (Group I) and 16 patients with aortic stenosis, left ventricular hypertrophy and normal coronary arteries (Group II). The hyperemic response in Groups I and II was 73.3 ± 2.2 and 65.8 ± 9.1 percent, respectively (difference not significant). Group II was subdivided into two groups: Group IIA had five patients with a left ventricular mass of less than 200 g (mean 158.8 ± 25.9); this group had a hyperemic response of 102.3 ± 9.9 percent. Group IIB had 11 patients with a left ventricular mass of more than 200 g (mean 308.9 ± 22.5) and a hyperemic response of 49.27 ± 10.42 percent. The hyperemic response was correlated with the diastolic left ventricular-aortic gradient ($r = +0.64$, $p < 0.001$), left ventricular mass ($r = -0.51$, $p < 0.01$) and aortic diastolic pressure ($r = +0.636$, $p < 0.001$). Group I had a left ventricular mass similar to that of Group IIA (124.9 ± 9 and 158.8 ± 26 g, respectively) but a lower hyperemic response (73.3 ± 2 and 102.3 ± 10 percent, respectively).

These data suggest that severe left ventricular hypertrophy is associated with a reduction in coronary vascular reserve; it is speculated that this decrease in the vascular reserve capacity may be related to the ischemic component of hypertrophic heart disease.

Under physiologic conditions, coronary blood flow can increase 2 to 4 times to meet the increased myocardial oxygen requirements associated with exercise or other stresses.[1] This constitutes the most important reserve mechanism, because the myocardial oxygen extraction is large (±75 percent) under resting conditions[2] and further oxygen availability is limited upon increased demands.

In chronic left ventricular hypertrophy, coronary blood flow per unit mass of myocardium has been found normal at rest.[3–6] Histopathologic studies[7–9] have demonstrated that the myocardial fiber to capillary ratio remains unchanged, with a consequent decrease in the observed capillary density. If hyperplasia of the coronary vasculature is inappropriate or nonexistent, the increase in coronary blood flow required to keep the normal flow per gram of myocardium can only be achieved by coronary vasodilation. If this occurs, the coronary vascular reserve would be limited and this effect would be more profound in the deep subendocardial layers of the myocardium.

It has been demonstrated[10] that the injection of contrast agent into the left coronary artery causes a significant increase in coronary flow.

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This increase in flow, or hyperemic reaction, represents vasodilation and decreased coronary vascular resistance. In this study the coronary vascular reserve was evaluated in patients with left ventricular hypertrophy secondary to aortic stenosis, by analysis of the hyperemic reaction to injection of contrast medium into the coronary arteries.

Methods

Patient selection: Twenty-five patients undergoing diagnostic cardiac catheterization and coronary angiography for chest pain syndrome or aortic stenosis were studied. There were 14 men and 11 women, aged 33 to 74 years (mean 56). All patients had normal coronary arteries as defined by selective coronary arteriography.

The control group (Group I) had nine patients. They all had chest pain syndrome and normal findings on catheterization and echocardiography. Group II had 16 patients with aortic stenosis undergoing catheterization for preoperative evaluation or for determination of the severity of the stenosis. This group was further divided into Groups IIA and IIB according to left ventricular mass.

It is recognized that the weight of a normal left ventricle in adults is 203 g or less in men and 141 g or less in women.[11] Accordingly, Group II was divided into Group IIA (mass less than 203 g for men or 141 g for women) and Group IIB (mass greater than 203 g for men and 141 g for women).

Cardiac catheterization: All patients signed informed consent before cardiac catheterization and agreed to have coronary sinus flow measurements performed, according to a protocol approved by the Mount Sinai Medical Center Research Administrative Committee.

Patients were premedicated with 10 mg of oral diazepam and fasted for at least 10 hours before catheterization. Under local anesthesia with 1 percent lidocaine (Xylocaine®), cutdown was performed in the right antecubital fossa. Coronary sinus flow studies were always performed before diagnostic catheterization. After systemic heparinization, a Sones catheter was introduced through the right brachial artery, and pressures were measured in the aorta and the left ventricle. One selective injection of contrast medium was performed into the right and left coronary arteries. It was estimated that sufficient time elapsed between the initial coronary injections (5 cc into the left and 3 cc into the right coronary artery) and the start of coronary flow measurements, so that no residual effect on the coronary flow or the hemodynamic variables would remain.

If no coronary disease was present, a multithermistor thermodilution catheter was introduced into the coronary sinus for measurement of coronary sinus flow; the position of the coronary sinus catheter was verified under fluoroscopy by injection of 2 to 3 ml of contrast medium. Resting coronary sinus flow was then recorded. While coronary sinus flow was being obtained, a hand injection of 5 to 10 ml of 76 percent Renografin® (meglumine diatriazoate) was performed to obtain full opacification of the left coronary artery; the hyperemic response that followed was recorded. Measurement continued until the coronary sinus flow returned to baseline. In 10 patients the dose-response effect of the contrast agent was studied by repeated, alternating injections of 5 and 10 ml of 76 percent Renografin.

No deep inspiration or holding of respiration was requested from the patient during this injection to avoid the shift in baseline. A demand pacemaker connected to the coronary sinus catheter electrodes was set at five beats less than the resting heart rate to avoid the bradycardia induced by the injection of contrast medium. The patient was in the supine position. The same procedure was repeated at least three times in each patient, with an interval of 3 to 8 minutes between each dye injection.

After these initial measurements, the coronary sinus flow catheter was withdrawn and diagnostic cardiac catheterization proceeded in the usual fashion. All studies were performed before diagnostic cardiac catheterization. No complications resulted from this procedure in this group of patients.

Recordings and measurements: *Voltage in the electrocardiogram* was measured by adding the voltages of the R wave in lead I plus the S wave in lead III and the voltages of the S wave in lead V_1 or V_2 plus the R wave in lead V_5. S-T segment depression with T wave inversion in leads V_4, V_5, and V_6, the so-called "strain pattern"[12] (Fig. 1), was noted when present.

Left ventricular and aortic pressures were recorded with the Sones catheter and a P23D Statham transducer. In nine cases these pressures were also recorded with a high fidelity Millar catheter. Left ventricular and aortic systolic pressures were measured as peak systolic pressures. Left ventricular mean diastolic pressure was calculated as an average of three points in diastole: initial, mid and late diastole. Left ventricular end-diastolic pressure was measured at the top of the R wave. Aortic diastolic pressure was measured as end-diastolic pressure. Left ventricular aortic systolic gradient was calculated as the difference between peak left ventricular and peak aortic systolic pressure. Left ventricular-aortic diastolic gradient was calculated as the difference between peak left ventricular and peak aortic systolic pressures. Left ventricular-aortic diastolic gradient was calculated as the difference between mean left ventricular diastolic pressure and aortic diastolic pressure. Cardiac output was determined by thermodilution technique with a 7 French Swan-Ganz catheter. Aortic valve area was calculated using the formula of Gorlin and Gorlin.[13]

Echocardiograms were performed just before catheterization or 1 day before. Patients with less than optimal tracings were not entered into the study. The thickness of the

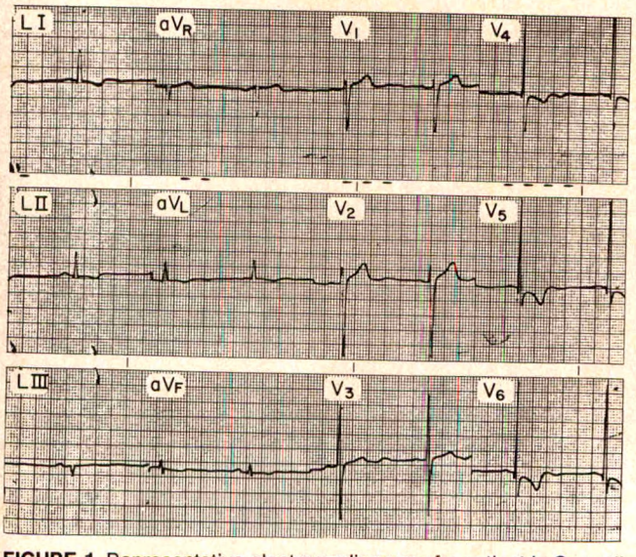

FIGURE 1. Representative electrocardiogram of a patient in Group II showing left ventricular hypertrophy and a "strain pattern."

septum (IVS_d) and the left ventricular posterior wall ($LVPW_d$) were measured in millimeters using the standard convention,[14] which includes the endocardium in the measurement; they were measured in diastole, before the *a* wave; the dimension of the left ventricular cavity was measured at this same point in diastole ($LVID_d$). Left ventricular (LV) mass was calculated using this formula[14]: LV mass (g) = $0.77 \times 10^3 [(LVID_d + LVPW_d + IVS_d)^3 - (LVID_d)^3] + 2.4$.

Coronary sinus blood flow was determined with the continuous thermodilution technique of Ganz et al.,[15] using a preshaped coronary sinus catheter with two thermistors and two pacing electrodes (Wilton Webster Laboratories). Coronary sinus flow at rest was obtained before any intervention. Hyperemic flow was defined as the maximal flow recorded after the injection of contrast medium into the left coronary artery. Percent increase in coronary sinus flow was calculated as follows: [(Hyperemic flow − Resting flow)/Resting flow] ×100. The position of the coronary sinus catheter was verified under fluoroscopy by injection of 2 to 3 ml of contrast medium and by cinearteriography during the venous phase of each injection into the left coronary artery. If the posterior interventricular vein drains very near the right atrium, its flow might not be included in the reading obtained by this technique[15]; whereas, if the thermistor is very close to the drainage site of the coronary sinus, it is more likely to have right atrial contamination, especially if right atrial pressure is elevated.[16] In addition, the position of the catheter may vary during the study or it may purposely be placed further into the coronary sinus if its position is not stable. For these reasons, the absolute values of coronary sinus flow were considered not to represent accurately total left ventricular venous outflow. Instead, the percent change in coronary sinus flow during hyperemia was analyzed.

Data from the coronary sinus flow measurements were recorded on an Electronics for Medicine recorder at a paper speed of 2.5 or 5 mm/s (Fig. 2). Data were digitized using a graph pen sonic digitizer, and analyzed by a PDP 11/70 computer. Coronary sinus flow, left ventricular mass and percent increase in coronary sinus flow were calculated by computer. Echocardiographic dimensions were measured by another investigator without knowledge of the results of the sinus flow measurements.

Validation of method: Flow measurements obtained by the thermodilution technique were validated in the following manner: a Sarns roller pump that generates a pulsatile flow was connected to a thermostatically controlled saline bath at 36.5°C and to a gradated empty glass container by a 3/8 inch (0.92 cm) Silastic® transparent tubing. Flow per minute was measured by timed collection into the gradated container. The thermodilution catheter was placed into the distal end of the Silastic tubing for flow determination. Forty-three measurements were made, with flow ranging from 70 to 810 ml/min. The correlation coefficient was +0.991 with a slope of 1.07 ± 0.02 ($b \pm S_b$).

Statistical analysis: Frequencies or means and standard errors were recorded for each measurement by groups: I, IIA and IIB. Overall comparisons among the three groups for all continuous measurements were made using analysis of variance. Pairwise comparisons (Group I versus II (A + B), Group I versus IIA, and so on) were made using Fisher's protected least significant difference technique[17] with $\alpha = 5$ percent. Pearson's product-moment correlation coefficients were calculated to determine the association of all continuous measurements with the percent change in coronary sinus flow. For the frequency-type data, Fisher's exact test[18] and the chi-square test were used. For the study comparing the hyperemic response to 5 ml versus 10 ml of the contrast agent, the paired *t* test was used.

Results

Clinical and hemodynamic data: Table I summarizes the clinical and hemodynamic data on these 25

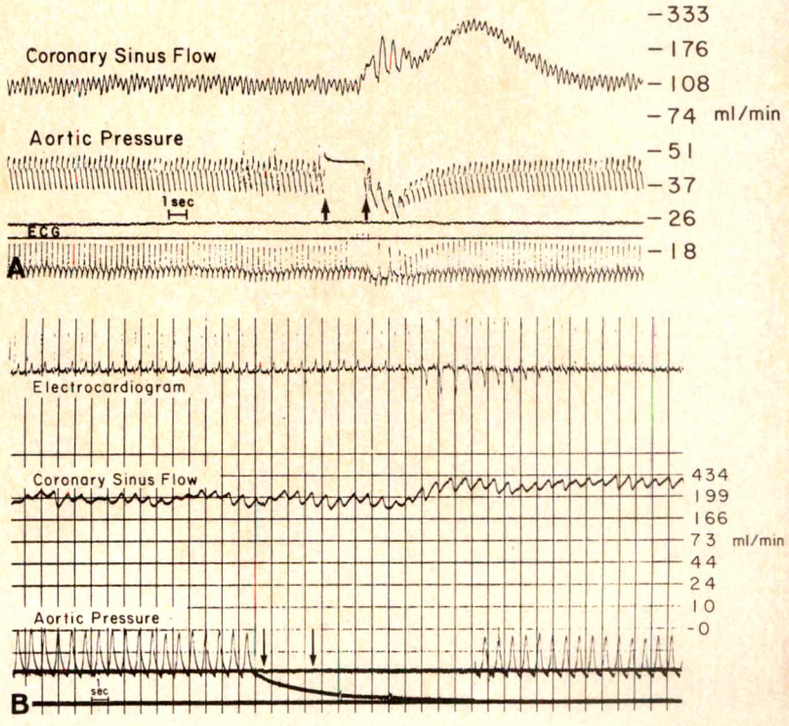

FIGURE 2. Coronary sinus flow tracings in a patient from Group I(**A**) and a patient from Group II(**B**). The **arrows** indicate the time of coronary arterial injection with contrast agent, which is followed by the hyperemic response. The coronary flow scale for each case is shown on the **right.** ECG = electrocardiogram.

TABLE I

Clinical and Hemodynamic Features of 25 Patients (mean ± standard error of the mean)

	Group I	Group II	Group IIA	Group IIB
Patients (n)	9	16	5	11
Age (yr)*,†	47.1 ± 2.47	61.2 ± 2.41	53.4 ± 4.83	64.8 ± 2.1
Angina*	3 of 9	11 of 16	2 of 5	9 of 11
ST-T "strain"*	0 of 9	11 of 15	2 of 4	9 of 11
R in V_1 + S in V_3 (mm)*,†	8.9 ± 2.22	18.9 ± 2.43	18.0 ± 1.29	19.3 ± 3.18
S in V_1 or V_2 + R in V_5 (mm)*,†	29.2 ± 2.27	37.8 ± 2.20	30.5 ± 3.28	41.0 ± 1.90
Heart rate (beats/min)	73.2 ± 2.96	70.3 ± 2.57	74.2 ± 3.75	68.5 ± 3.29
LV systolic (mm Hg)*,†	123.7 ± 5.89	207.1 ± 7.01	188.6 ± 11.60	215.5 ± 7.76
LV mean diastolic (mm Hg)*,†	5.4 ± 1.41	11.9 ± 1.25	10.4 ± 1.75	12.6 ± 1.64
LV end-diastolic (mm Hg)*,†	11.2 ± 1.39	22.6 ± 1.96	21.4 ± 2.09	23.2 ± 2.74
Ao systolic (mm Hg)	121.4 ± 6.46	127.1 ± 4.21	137.6 ± 8.32	122.3 ± 4.35
Ao diastolic (mm Hg)*	72.4 ± 3.18	69.5 ± 2.54	81.0 ± 2.92	64.3 ± 1.97
Ao diastolic − LV diastolic (mm Hg)*,†	67.0 ± 2.75	57.6 ± 2.99	70.6 ± 3.12	51.6 ± 2.54
Ao valve gradient (mm Hg)	. . .	80.1 ± 7.73	51.4 ± 10.81	93.1 ± 7.39
Ao valve area (cm^2)	. . .	0.7 ± 10.0	1.1 ± 0.20	0.5 ± 0.05
IVS (mm)*,†	9.9 ± 0.31	15.2 ± 7.0	12.1 ± 0.81	16.6 ± 0.56
LVPW (mm)*,†	10.0 ± 0.37	14.7 ± 0.69	11.9 ± 0.84	16.0 ± 0.61
LVID (mm)*	41.0 ± 1.11	43.9 ± 1.92	38.4 ± 0.75	46.5 ± 2.42
LV mass (g)*,†	124.9 ± 9.41	258.0 ± 24.85	158.8 ± 25.94	308.9 ± 22.53
CSF, rest (ml/min)*,†	145.3 ± 22.28	226.7 ± 26.86	146.3 ± 8.91	257.6 ± 33.86
CSF, hyperemia (ml/min)	251.9 ± 39.41	364.7 ± 43.6	314.4 ± 41.6	387.6 ± 60.56
CSF, percent change*	73.3 ± 2.16	65.8 ± 9.11	102.3 ± 9.93	49.3 ± 10.42

* $p < 0.05$ by analysis of variance for groups I, IIA and IIB. † $p > 0.05$ by analysis of variance for groups I and II.
Ao = aorta; CSF = coronary sinus flow; IVS = interventricular septum; LVID = left ventricular internal diameter; LVPW = left ventricular posterior wall; R in V_1 + S in V_3 = the sum of voltages of the R wave in lead V_1 and the S wave in lead V_3; S in V_1 or V_2 + R in V_5 = the sum of voltages of the S wave in lead V_1 or V_2 and the R wave in lead V_5.

patients by patient groups: I (control subjects), IIA (patients with aortic stenosis with normal left ventricular mass), IIB (patients with aortic stenosis with abnormal left ventricular mass) and II (A + B). The significant findings which are consistent when one compares the control group (Group I) with the total group with aortic stenosis (Group II) or with the two separate groups (IIA and IIB) are as follows:

The patients with aortic stenosis were older, with significantly higher values for electrocardiographic voltage (S wave in lead V_1 or V_2 + R wave in lead V_5), left ventricular systolic, mean diastolic and end-diastolic pressures, interventricular septal and posterior wall thickness and left ventricular mass on echocardiography, and coronary sinus flow at rest. They had a significantly smaller diastolic gradient across the aortic valve (aortic diastolic-left ventricular diastolic pressure) than did control patients [$F(2,22) = 13.29$ ($p < 0.1$)].

Angina occurred in 3 (33.3 percent) of the 9 control patients compared with 11 (68.7 percent) of the 16 patients in Group II, a statistically significant difference ($p < 0.5$) by Fisher's exact test. An ST-T "strain" pattern occurred in none of the control patients (Group I) but in 11 (73.3 percent) of 15 patients in Group II ($p < 0.01$) by Fisher's exact test. Seven of these 11 patients were taking digitalis, 1 had left bundle branch block and 3 had right bundle branch block.

Comparisons among Groups I, IIA and IIB disclosed three additional significant results: The percent change in coronary sinus flow was significantly different among groups [$F(2,22) = 7.69$, $p < 0.01$]. The percent change in coronary sinus flow in Group IIB (49 percent) was significantly smaller than that in Group I (73 percent) or Group IIA (102 percent). Aortic diastolic pressure was significantly lower in Group IIB (64.17 mm Hg) than that in Group I (72.44 mm Hg) or Group IIA (81.00 mm Hg) [$F(2,22) = 4.02$, $p = 0.03$]. The echocardiographic left ventricular internal dimension in Group IIB (46.5 mm) was significantly larger than that in Group I (41.0 mm) or Group IIA (38.4 mm) [$F(2,22) = 4.02$, $p = 0.03$].

Coronary sinus flow with hyperemia: Table II indicates the correlation of the percent change in coronary sinus flow with hyperemia (coronary vascular reserve) and 11 variables that may influence it for all 25 patients. There was a strong negative correlation be-

TABLE II

Correlations of Percent Change in Coronary Sinus Flow and 11 Other Variables

	r	p
Heart rate	+0.276	<0.18
LV-aortic systolic gradient	−0.380	<0.05*
LV systolic pressure	−0.230	<0.257
Aortic systolic pressure	+0.357	<0.08
Aortic-LV diastolic gradient	+0.643	<0.0005*
LV diastolic pressure	−0.203	<0.33
Aortic diastolic pressure	+0.636	<0.0006*
LV mass	−0.514	<0.0086*
IVS_d	−0.416	<0.0388*
$LVPW_d$	−0.407	<0.0437*
$LVID_d$	−0.412	<0.0407*

* Statistically significant ($p < 0.05$).
IVS_d = the thickness of the septum in diastole; $LVID_d$ = the dimension of the left ventricular cavity in diastole; $LVPW_d$ = the thickness of the left ventricular posterior wall in diastole; LV = left ventricular; p = probability; r = correlation coefficient.

tween percent change in flow and left ventricular mass and left ventricular-aortic systolic gradient. There was a positive correlation between the percent change in flow and the left ventricular-aortic diastolic gradient. In each case, the crucial components of these relations were the aortic systolic pressure in the left ventricular-aortic systolic gradient, and the aortic diastolic pressure in the left ventricular-aortic diastolic gradient. There was an inverse correlation between myocardial mass and percent change in coronary flow with hyperemia. A patient with severe aortic stenosis and the highest value for myocardial mass had no hyperemic reaction; this patient had the highest resting coronary flow (485 ml/min).

When the reproducibility of the coronary sinus flow data was analyzed, the coefficient of variation for flow at rest and during hyperemia was 7.1 and 9.51 percent, respectively.

Discussion

Ventricular Hypertrophy and Coronary Blood Flow

Increased myocardial oxygen delivery is normally attained by an increase in coronary blood flow, with little if any contribution from an increase in oxygen extraction.[1] In left ventricular hypertrophy secondary to pressure or volume overload, cardiac work and oxygen consumption are chronically increased with a proportional increase in coronary blood flow so that coronary blood flow and myocardial oxygen consumption per unit weight of myocardium remain normal at rest.[3–6] This increase in flow can be obtained either by dilatation of the existing coronary vasculature or by an absolute increase in the cross-sectional area of the vascular bed (neovascular growth).

Animal experiments[19–21] have suggested that left ventricular hypertrophy is associated with decreased coronary vascular reserve, determined by a failure of the coronary vascular resistance to decrease as the myocardial mass increases. Clinical studies in patients with aortic stenosis have shown an inappropriate increase in coronary blood flow secondary to isoproterenol infusion[22,23] and evidence of myocardial hypoxia (lactate production) on rapid atrial pacing.[24]

Ventricular hypertrophy and coronary vascular reserve (response to hyperemia): We studied coronary vascular reserve by analyzing the hyperemic response to selective injection of contrast agent into the coronary arteries. Sixteen patients (Group II) had left ventricular hypertrophy secondary to aortic stenosis and 9 (Group I) had chest pain syndrome with normal coronary arteries. Although the hyperemic response was similar in Groups I and II (73.3 ± 2.16 and 65.8 ± 9.11, respectively), an interesting difference was noted within Group II. Five patients (Group IIA) had aortic stenosis with a mild increase in left ventricular mass, not beyond the established upper limit of normal[16] (mean 158.8 ± 25.9 g). These patients had the highest hyperemic response in the study group (102.3 ± 9.9 percent increase in flow). Group IIB had 11 patients with a mean left ventricular mass of 308.9 ± 22.5 g; the hyperemic response in Group IIB (49.3 ± 10.4) was significantly lower than in Group IIA ($t = 4.63$, $p < 0.01$) and also significantly lower than that in Group I ($t = 2.10$, $p < 0.05$). For the entire cohort of 25 patients, left ventricular mass was inversely correlated with coronary vascular reserve ($r = -0.514$, $p < 0.0086$). The patient with the highest left ventricular mass (411 g) had a very high resting coronary sinus flow and had no further increase in flow after the injection of contrast agent, evidence suggestive of exhausted coronary vascular reserve. Coronary vascular reserve was also found to be decreased in relation to a decreased left ventricular-aortic diastolic gradient ($r = +0.643$) and to a reduced aortic diastolic pressure ($r = +0.636$); wall thickness as determined echocardiographically had an inverse relation with coronary vascular reserve ($r = -0.421$) (Table II). Thus our data support the concept that left ventricular hypertrophy is associated with a decrease in coronary vascular reserve.

Mechanisms of decreased coronary vascular volume: Our findings of a decreased coronary vascular reserve can be explained by previous experimental observations in left ventricular hypertrophy that have shown (1) the presence of vascular hyperplasia (new vessel formation),[25] although insufficient to keep a normal capillary density in the myocardium[7–9]; (2) vascular intramural changes (hypertrophy of the vessel wall) that could reduce the vascular capacitance of the resistance vessels[20,26]; (3) increased tone of the coronary vessels, related to humoral factors, myogenic constriction[27] or increased alpha-adrenergic stimulation[28]; and (4) increased myocardial tissue pressures during diastole that may increase coronary vascular resistance.[29]

Myocardial ischemia in aortic stenosis: If the hypertrophic myocardium of patients with aortic stenosis has a limited coronary vascular reserve, myocardial ischemia will occur under circumstances of increased demand. The subendocardium will tend to suffer from ischemia first[30] because the subendocardium is perfused for a shorter time in each cardiac cycle,[31] or because the oxygen consumption in the subendocardium is higher than in the subepicardium,[32] or for other yet unclear reasons. We postulate that the electrocardiographic changes of left ventricular hypertrophy traditionally called the "strain pattern"[12] may reflect the acute or chronic effects of subendocardial ischemia; in our study a "strain pattern" in the electrocardiogram was present in 9 of 11 patients in Group IIB (the other 2 patients in Group IIB had right bundle branch block). The occurrence of myocardial ischemia in patients with aortic stenosis and left ventricular hypertrophy is also suggested by the common clinical observation of angina pectoris in the absence of obstructive coronary artery disease.[33] In our study, 9 of 11 patients in Group IIB had angina pectoris. Further evidence of the tendency for ischemia to develop in patients with aortic stenosis and left ventricular hypertrophy is provided by the demonstration of lactate production during stimulation with isoproterenol.[23]

The clinical deterioration of patients with left ventricular hypertrophy may very well be related to left

ventricular failure secondary to ischemia (acute or chronic). Experimental studies[34] have proved that myocardial function deteriorates when the subendocardium is underperfused transiently and that return of normal perfusion is accompanied by recovery of left ventricular function. That underperfusion may be reversible in patients with left ventricular hypertrophy and aortic stenosis is suggested by studies done 6 months after aortic valve replacement, showing that lactate production after isoproterenol infusion no longer occurs.[23]

Possible Limitations of the Study

Coronary sinus flow measurement may not represent total left ventricular venous outflow: It has been shown that in the human heart, coronary sinus flow is highly representative of the total left ventricular efflux.[35,36] It has also been shown that coronary sinus flow as determined by the continuous thermodilution technique accurately represents total left ventricular coronary flow.[37,38] A possible source of error in the estimation of total coronary sinus flow is the fact that in some cases the posterior ventricular vein drains very near the ostium of the coronary sinus, and its flow is not included in the measurements obtained.[15] The flow measured decreases artifactually if the thermodilution catheter is advanced too far into the coronary sinus or increases artifactually if it is too close to the right atrium, especially in cases with increased right atrial pressure.[16]

These considerations would not influence the conclusions of our study since our analysis was based not on the total flow itself, but rather on the percent change in flow seen during hyperemia induced by the injection of contrast agent. The percent change should be the same for total and less than total coronary sinus flow.

Contrast agents may not induce maximal coronary vasodilation: A major limitation in our study could exist if the contrast agent produced less than maximal increase in coronary conductance, because in that case the total coronary vascular reserve could not be evaluated by this method. Existing information is controversial in this respect. The increase in coronary conductance produced by a contrast agent is equivalent to a 10 to 15 second occlusion of the coronary artery ($r = 0.86$)[39,40] and similar to the effect of an intracoronary bolus injection of adenosine triphosphate or papaverine[39] but less than the effect of a prolonged infusion of these agents.[39] The hyperemic reaction to injection of contrast agent is greater than the increased flow necessary to repay the oxygen debt, as proved by an increase in coronary sinus oxygen saturation without a change in myocardial oxygen consumption[41] and a concomitant increase in the forearm flow,[42] suggesting an important reflex component in the contrast agent-induced hyperemia.

Although the effect of contrast agents on coronary conductance may produce near-maximal vasodilation, the effects of contrast agents on cardiac and circulatory hemodynamics[43,44] may influence the hyperemic reaction qualitatively and quantitatively, and maximal coronary flow may not be obtained. Agents that increase coronary conductance without major changes in hemodynamic variables seem better suited for the study of coronary reserve in human subjects. We are currently preparing a study with such an agent, intravenous dipyridamole.

The increase in flow secondary to fast pacing (140/min through electrodes located in the coronary sinus thermodilution catheter) was measured in eight patients and found to be equal to or lower (never greater) than the hyperemic flow induced by the contrast agent. Rapid pacing produced important hemodynamic changes in patients with aortic stenosis and did not seem appropriate for the study of the coronary vascular reserve in these patients.

Even if the contrast agent had not induced maximal increase in coronary sinus flow in our study, the analysis of the directional changes observed in Groups I, IIA and IIB seem valid, as well as the analysis of the factors determining such a change (such as left ventricular dimensions and hemodynamic variables).

Dose response to contrast agent: If the hyperemic response was dose-related, the hypertrophic ventricle would receive a lower dose of contrast agent per gram of myocardium if the amount injected was always the same. In our study, patients received a bolus dose of 76 percent Renografin, sufficient to opacify clearly the entire left coronary artery (5 to 10 ml).

A similar hyperemic reaction has been reported when 3 to 10 ml of contrast agent is injected.[39,45] In our study, injection of 1 to 2 ml of contrast agent was associated with a minimal or absent hyperemic response. Five versus 10 ml injections were tested on repeated random measures in 10 patients. Calculations of the resting and hyperemic coronary sinus flow were done blindly in these cases, without knowledge of the dose injected. There was no statistically significant difference between the hyperemia (percent change) induced by the two volumes of injectate (paired $t = 1.86$, difference not significant). It seems unlikely that the results obtained in our study were artifactually influenced by a dose-response effect.

Determinants of coronary flow not studied: Important determinants of coronary flow, such as the duration of systole and diastole, were not specifically analyzed in this study. These may have a major influence on coronary vascular reserve.

Control group: Nine patients with chest pain syndrome found to have normal coronary arteries and normal left ventricular function served as control subjects in our study. Our results showed that this group had a lower coronary reserve than that of patients with aortic stenosis and mild or no hypertrophy (Group IIA) ($t = -2.04$, $p = 0.06$). Preliminary information in the form of an abstract[46] proposes that a decrease in coronary vascular reserve may be related to the pathogenesis of chest pain in these patients. On the other hand, patients in an initial phase of left ventricular hypertrophy

(Group IIA) may have an increased coronary reserve capacity.

A decreased coronary vascular reserve in Group I may explain why we found no difference in the coronary reserve of Groups I versus II. However, our conclusions regarding the correlation of the coronary vascular reserve with other variables (such as left ventricular mass and hemodynamic variables) are still valid, and appear most relevant when comparing Groups IIA and IIB. Further studies appear necessary, in which a group with "normal" coronary vascular reserve can be analyzed and used as a control group. A truly normal group may be difficult to obtain because such patients rarely undergo diagnostic cardiac catheterization.

Implications: Our study shows that patients with left ventricular hypertrophy secondary to aortic stenosis have a decrease in coronary vascular reserve, proportional to the increase in left ventricular mass and the decrease in left ventricular-aortic diastolic gradient and in aortic diastolic pressure. We speculate that this decrease in coronary vascular reserve may be related to the ischemic components of left ventricular hypertrophy. Further investigation seems necessary to clarify and expand the findings of this study.

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Assessment of Left Ventricular Function by Radionuclide Angiography During Induced Supraventricular Tachycardia

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Electrocardiographically synchronized radionuclide angiography was performed before, during and after induced paroxysmal supraventricular tachycardia in 13 patients. Data were acquired with a computer-interfaced Anger camera in a left anterior oblique projection. No data were acquired during tachycardia until tachycardia had been sustained for 1 minute. Patients ranged in age from 20 to 64 years (mean ± standard deviation 42 ± 14.5). Three patients had organic heart disease and 10 did not. Baseline and tachycardia heart rates (beats/min) were 59 to 99 (73 ± 11) versus 141 to 228 (157 ± 22). Baseline and tachycardia left ventricular measurements (mean ± standard error) were as follows: ejection fraction 64 ± 2 versus 62 ± 4 percent (not significant), ejection rate 3.0 ± 0.1 versus 4.3 ± 0.4 mean ventricular counts/s ($p < 0.001$), normalized end-diastolic counts 72.7 ± 7.8 versus 48.7 ± 6.7 × 10^3 counts ($p < 0.001$), normalized stroke counts 37.1 ± 3.4 versus 23.3 ± 2.7 × 10^3 counts ($p < 0.001$) and normalized count cardiac output 2,717.5 ± 273.0 versus 3,620.2 ± 403.7 × 10^3 counts/min ($p < 0.005$). Although ejection fraction for the whole group did not change significantly, it decreased during tachycardia by 5 percentage points or more in five patients. These were the three patients with heart disease and the two normal patients with the fastest heart rate during tachycardia (228 and 214 beats/min, respectively).

In summary, paroxysmal supraventricular tachycardia was characterized by a marked decrease in left ventricular end-diastolic and stroke volumes but increased ejection rate and cardiac output without significant change in ejection fraction. Heart disease or rapid heart rate during tachycardia appeared to have a deleterious effect on ejection fraction.

Paroxysmal supraventricular tachycardia is a common arrhythmia, often accompanied by symptoms and signs of hemodynamic embarrassment. However, only few data are available concerning its hemodynamics. There exist several case reports of hemodynamic data obtained when tachycardia occurred fortuitously in the course of cardiac catheterization.[1–7] In addition, two larger series were recently reported concerning tachycardia induced under controlled conditions, so that planned hemodynamic observations could be made.[8,9] In all of the aforementioned studies, the resulting data consisted of blood pressures, atrial pressure tracings, stroke volume and cardiac output with a major emphasis on the period immediately after the onset of tachycardia and less emphasis on steady state. There are a few direct data on left ventriclar volume, ejection fraction and wall motion during tachycardia.

The development of nuclear angiography has made possible evaluation of these measurements of left ventricular function both at rest and during exercise.[10–12] In this study, we report nuclear angiographic findings in 13 patients in whom imaging was performed before, during and after sustained paroxysmal supraventricular tachycardia.

Methods

Study patients: The following criteria were used in the selection of patients for this study: (1) history of documented recurrent paroxysmal supraventricular tachycardia, (2) ability to induce and terminate sustained tachycardia reliably

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in the electrophysiology laboratory, (3) presence of a radiofrequency pacemaker (2 patients) or temporary pacing catheter (11 patients) during chronic drug study enabling induction and termination of tachycardia in the nuclear medicine laboratory, (4) signing of informed consent. No attempt was made to restrict the study to patients with the presence or absence of a specific symptom complex during tachycardia. The mechanism of tachycardia was established during intracardiac electrophysiologic study using previously published criteria.[13]

Thirteen patients, aged 20 to 60 years (mean ± standard deviation, 42 ± 14.5) had radionuclide angiography during tachycardia; 7 were women and 6 were men. Ten of the 13 patients had no evident organic heart disease, 1 patient (Case 11), had aortic valve insufficiency, 1 (Case 12) had corrected transposition of the great vessels with a ventricular septal defect and one (Case 13) had restrictive cardiomyopathy. Eleven patients were taking no cardioactive medications during the study. One patient (Case 11) was taking propranolol, 40 mg orally three times daily, and one (Case 6) was taking disopyramide, 300 mg orally every 6 hours. Neither drug interfered with induction of tachycardia.

The mechanism of the tachycardia as defined by intracardiac electrophysiologic study was atrioventricular (A-V) reentrance using an anomalous pathway for retrograde conduction in seven patients, A-V nodal reentrance in five and atrial reentrance in one.

Nuclear angiography: Electrocardiographically gated, equilibrium nuclear angiography was performed using an in vivo red blood cell labeling method with 18 to 25 mCi of technetium-99m.[14] A large field Anger camera (Searle LFOV) was positioned for a left anterior oblique view with the patient supine. Data were recorded and analyzed on an Informatek Simis 3 computer.

A baseline study was acquired while the patient had sinus rhythm. With this completed, tachycardia was induced by cardiac stimulatory techniques. No data were acquired for the 1st minute after induction of tachycardia to allow for stabilization of cycle length and to avoid previously described early hemodynamic effects[8] that are not prolonged enough for assessment by this technique. With no change in the position of the patient or the camera, a complete study was performed during tachycardia, after which tachycardia was terminated with pacing. One patient had a second study during tachycardia after atropine, 1 mg intravenously. When each patient's pulse and blood pressure had returned to baseline values (within 5 to 10 minutes), a post-tachycardia study was performed (10 of 13 patients). Again, the position of the patient and camera were unchanged.

Data were acquired before, during and after tachycardia for a total of 5 to 10 minutes for each of the three studies. Blood pressure (cuff method), the electrocardiogram and symptoms were monitored and recorded during the three data acquisition periods.

Processing of data: The equilibrium gated acquisition was stored in 16 frames of 64 by 64 matrix resolution. Ejection fraction was calculated using a program based on three regions of interest: end-diastole, end-systole and perisystolic background. The end-diastolic region of interest is drawn semiautomatically, with the septum and valve plane hand-drawn using the stroke volume image (end-diastole minus end-systole) as a guide. This procedure aids both reproducibility and exclusion of the left atrium from the region of interest. The protocol was previously described for first transit studies[15] and was validated for gated studies in this laboratory (for 17 patients with an ejection fraction of 26 to 81 percent the correlation coefficient with biplane contrast angiography was 0.85 [$p < 0.0001$]). Each study was processed independently, so that changes in ventricular volume and background level were taken into account. From the interpolated time-activity curve obtained in this protocol, the left ventricular ejection rate was calculated according to the method of Marshall et al.[16] and expressed in units of mean ventricular counts/s. Regional wall motion was evaluated by consensus among three experienced observers using the display of superimposed end-diastolic and end-systolic contours and three functional images: the stroke volume image, the paradox image (end-systole minus end-diastole) and the regional ejection fraction image.

Relative end-diastolic volumes (*end-diastolic counts*) were calculated using the total counts in the left ventricular region of interest at end-diastole after background correction. Relative stroke volumes (stroke counts) were calculated using only the end-diastolic region of interest and subtracting its contents at end-systole from its contents at end-diastole. No background subtraction was necessary for this calculation because only one region was used. Relative cardiac output (count cardiac output) was defined as the product of stroke counts times heart rate.

For comparison of the three studies on each patient, the end-diastolic counts must be normalized to the same counting time and corrected for decay. The counting time is the product of the frame length and the number of cycles acquired in the study, but a simple normalization can be made by using as reference the number of counts contained in the whole field of view in the end-diastolic frame of the baseline acquisition. If the subsequent acquisitions (during and after tachycardia) differ in number of cycles or frame duration, this difference will be reflected in the number of counts in the whole field of view. The correction factor calculated in this way also includes the decay factor, because decay tends to decrease the total number of counts during the second and third acquisitions.

This method of normalization could be validated for the last four patients studied (in whom the exact number of cycles acquired was available) by comparison with normalization to exact counting time with correction for decay. For these four patients, there was less than a 5 percent difference in the two normalization methods. It is clear that neither method allows comparison of volumes between patients.

Analysis of data: Statistical analysis was done using Student's *t* test for paired values (two-tailed). Tachycardia and post-tachycardia values for end-diastolic counts, stroke counts and count cardiac output were calculated for each patient as a percent of baseline values. This calculation was used for graphic and qualitative analysis only.

Results

Hemodynamics: Baseline Versus Tachycardia (Table I)

Heart rate (Fig. 1): Baseline heart rates ranged from 59 to 99 (mean ± standard error of the mean 73 ± 11) beats/min. Heart rates during tachycardia ranged from 141 to 228 (mean 157 ± 22) beats/min. Baseline systolic blood pressure ranged from 90 to 130 (mean 113 ± 14) mm Hg. During tachycardia, systolic blood pressure ranged from 72 to 130 (mean 102 ± 22) mm Hg (difference not significant [NS]). Only two patients, one with organic heart disease (Case 12) and one with a heart rate during tachycardia of 228 beats/min (Case 8), had a marked decrease in systolic blood pressure (from 105 to 82 and from 118 to 74 mm Hg, respectively). For these two patients, the cuff blood pressure during tachycardia was only palpable so no diastolic reading is available.

For the remaining patients, diastolic blood pressure ranged from 55 to 80 (mean 68 ± 8) during the baseline period versus 60 to 95 (mean 77 ± 13) mm Hg during tachycardia.

Ejection fraction (Fig. 1): For the entire group, baseline ejection fraction ranged from 53 to 76 percent (mean ± standard error of the mean 64 ± 2). During tachycardia, ejection fraction ranged from 37 to 76 percent (mean 62 ± 4) (NS). Four patients (and one additional patient after atropine) had a decrease in ejection fraction during tachycardia of more than 5 percentage points (see later). No patient had an increase in ejection fraction during tachycardia of more than 5 percentage points.

Baseline ejection rate for the entire group ranged from 2.1 to 4.9 (mean 3.0 ± 0.2) in units of mean ventricular counts/s. During tachycardia, ejection rate ranged from 1.7 to 7.0 (mean 4.3 ± 0.4) ($p < 0.001$) (Fig. 1). Ejection rate decreased during tachycardia in only two patients (see later).

End-diastolic ventricular volume (Fig. 2 and 3): Baseline relative end-diastolic volume, as estimated by normalized end-diastolic counts, ranged from 10.7 to 122.0 (mean 72.7 ± 7.8) thousand counts. During tachycardia, end-diastolic counts decreased in all patients to a range of 5.6 to 100.9 (48.7 ± 6.7) thousand counts ($p < 0.001$). The wide range of values for end-diastolic counts (as well as for stroke counts and count cardiac output) reflects the lack of standardization of baseline acquisition time early in the series. Thus comparison of normalized numbers of end-diastolic counts, stroke counts and count cardiac output, while appropriate for the three studies in the same patient, is not appropriate for comparing one patient with another. Expressed as a percent of baseline, normalized end-diastolic counts during tachycardia ranged from 43 to 91 percent (median 65 percent).

Stroke volume (Fig. 2 and 3): Baseline relative stroke volume, as estimated by normalized stroke counts, ranged from 5.4 to 52.6 (mean 37.1 ± 3.4) thousand counts. During tachycardia, stroke counts decreased in all patients to a range of 2.8 to 39.6 (mean 23.3 ± 2.7) thousand counts ($p < 0.001$). Expressed as a percent of baseline value, normalized stroke counts during tachycardia ranged from 47 to 89 percent, median 50 percent).

Cardiac output (Fig. 2): Baseline relative cardiac output, as estimated by normalized count cardiac output, ranged from 348 to 3,822 (mean 2,717.5 ± 273.0) thousand counts. During tachycardia, count cardiac output increased, although modestly, in all patients to a range of 441 to 6,091 (mean 3,620.2 ± 403.7) thousand counts ($p < 0.005$). Expressed as a percent of baseline value, normalized count cardiac output during tachycardia ranged from 105 to 182 percent (median 132 percent).

Wall motion: All the patients without organic heart disease had normal wall motion at rest and during tachycardia. One of three patients with organic heart disease (Case 12, with a previously repaired ventricular septal defect) had markedly abnormal septal motion

TABLE I
Summary of Clinical and Nuclear Angiographic Data

Case	Age (yr)	OHD	Heart Rate (beats/min)			Ejection Fraction (%)			Ejection Rate*			End-Diastolic Counts ($\times 10^3$)			Stroke Counts ($\times 10^3$)			Count Cardiac Output ($\times 10^3$)		
			Base	PSVT	Post	Base	PSVT	Post	Base	PSVT	Post	Base	PSVT	Post	Base	PSVT	Post	Base	PSVT	Post
1	30	−	73	141	70	74	76	73	3.7	5.5	3.6	47.7	25.8	43.8	24.6	16.8	26.6	1,795.8	2,361.8	1,860.6
2	57	−	85	148	88	68	72	69	3.6	4.7	3.8	57.9	44.4	51.4	32.6	25.0	29.6	2,768.5	3,693.1	2,600.9
3	64	−	66	147	78	66	69	69	3.1	4.9	2.8	61.3	39.3	53.5	35.3	21.1	30.3	2,332.9	3,106.3	2,361.9
4	51	−	64	155	...	61	63	...	2.9	4.4	...	10.7	5.6	...	5.4	2.8	...	347.5	441.3	...
5	53	−	83	148	85	67	68	65	4.9	7.0	4.7	103.2	54.5	116.2	52.6	31.2	60.3	4,361.7	4,619.5	5,123.8
6	20	−	75	154	74	64	66	61	2.7	3.6	2.5	82.0	65.0	103.3	44.7	39.6	52.6	3,351.0	6,090.7	3,893.2
7	35	−	73	170	...	65	70	...	2.7	4.1	...	59.9	25.6	...	30.8	14.5	...	2,247.7	2,472.9	...
8	20	−	99	228	103	60	46	62	2.7	3.6	2.8	74.5	53.7	81.3	38.6	19.0	42.3	3,822.4	4,334.3	4,361.0
9	59	−	76	145	79	76	75	75	3.5	5.4	3.6	60.6	49.2	69.4	42.6	35.0	49.9	3,236.8	5,075.9	3,944.5
10	47	−	67	153	62	57	69	54	2.2	4.7	2.1	79.9	45.7	79.2	41.8	27.9	38.6	2,803.3	4,267.2	2,392.6
11	41	+	60	158	68	66	57	65	3.1	3.7	3.0	96.4	43.9	94.8	42.6	20.6	44.8	2,556.0	3,258.0	3,045.2
12	30	+	59	151	65	54	39	46	2.2	2.1	1.9	122.0	100.9	130.9	52.6	30.7	50.6	3,104.0	4,634.2	3,288.4
13	41	+	68	148	...	53	37	...	2.1	1.7	...	88.3	80.0	...	38.2	18.3	...	2,599.6	2,706.9	...

* Measured in units of mean ventricular counts/s.
Base = baseline; OHD = organic heart disease; Post = after tachycardia; PSVT = paroxysmal supraventricular tachycardia; + = present; − = absent.

that persisted during tachycardia. A second patient with heart disease (Case 11) had no abnormality of wall motion at rest or with tachycardia. The third patient with heart disease (Case 13) had normal wall motion at rest but septal akinesia with tachycardia.

Tachycardia after atropine (Table II): One patient (Case 7) was given atropine, 1 mg intravenously, after the tachycardia study was completed. Tachycardia was reinduced and a second tachycardia study was acquired to reflect the faster heart rate after atropine (214 versus 170 beats/min). Ejection fraction during tachycardia after atropine decreased, both in relation to tachycardia before atropine (55 versus 70 percent) and in relation to the baseline value (55 versus 65 percent).

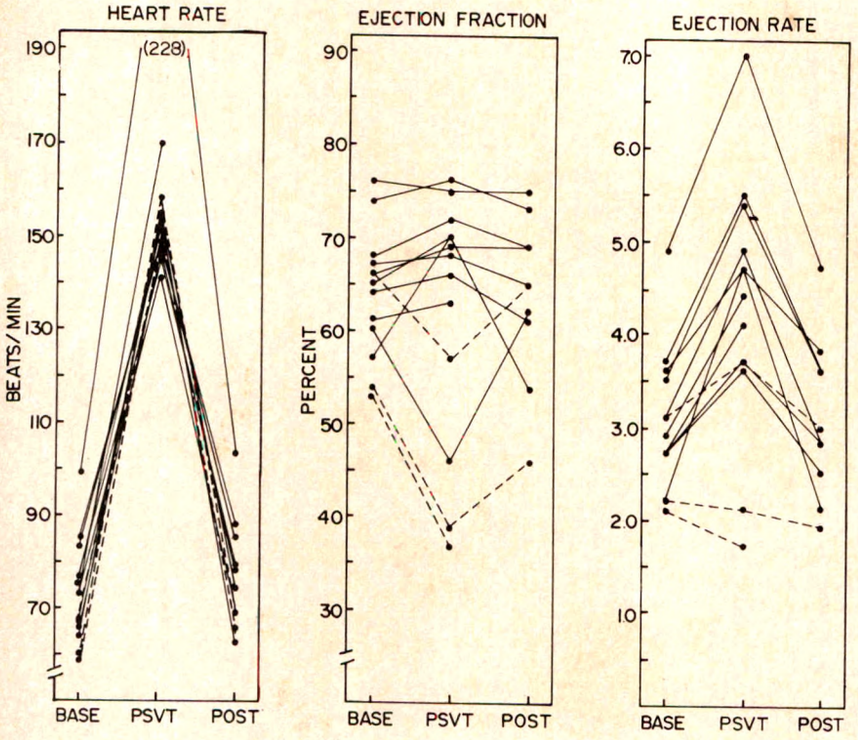

FIGURE 1. Heart rate (beats/min), ejection fraction (percent) and ejection rate (mean ventricular counts/s) before (BASE), during and after (POST) induced sustained paroxysmal supraventricular tachycardia (PSVT). Each **closed circle** represents one patient. The **dashed lines** identify the three patients with organic heart disease (Cases 11, 12 and 13).

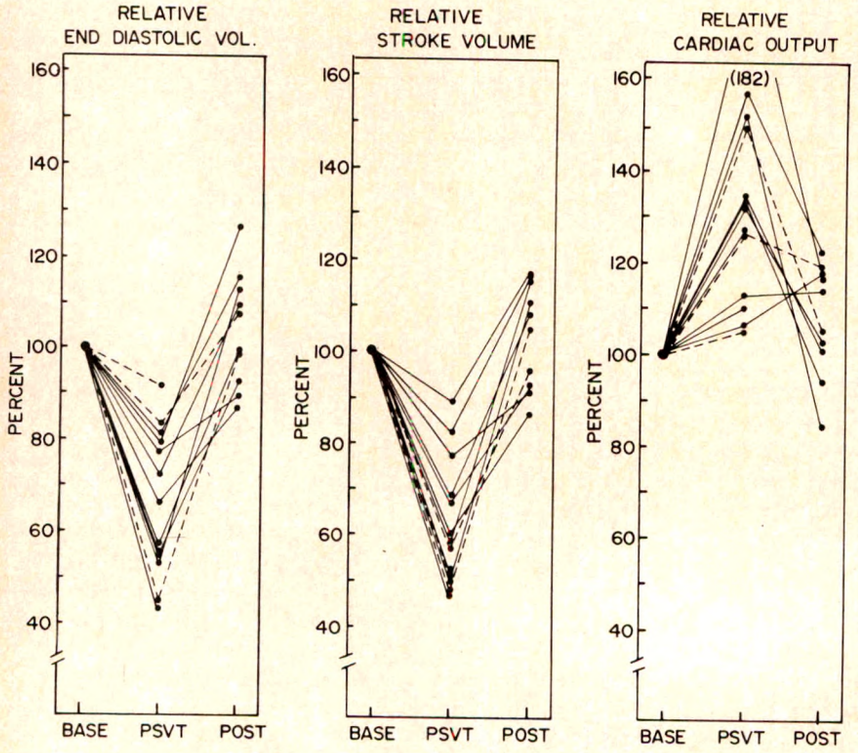

FIGURE 2. Relative end-diastolic volume (VOL.), stroke volume and cardiac output as measured by normalized end-diastolic counts, stroke counts and count cardiac output. Baseline values are defined as 100 percent. Paroxysmal supraventricular tachycardia (PSVT) and post-tachycardia values are expressed as a percent of baseline value (see text). Each **closed circle** represents one patient; the **dashed lines** identify the three patients with heart disease.

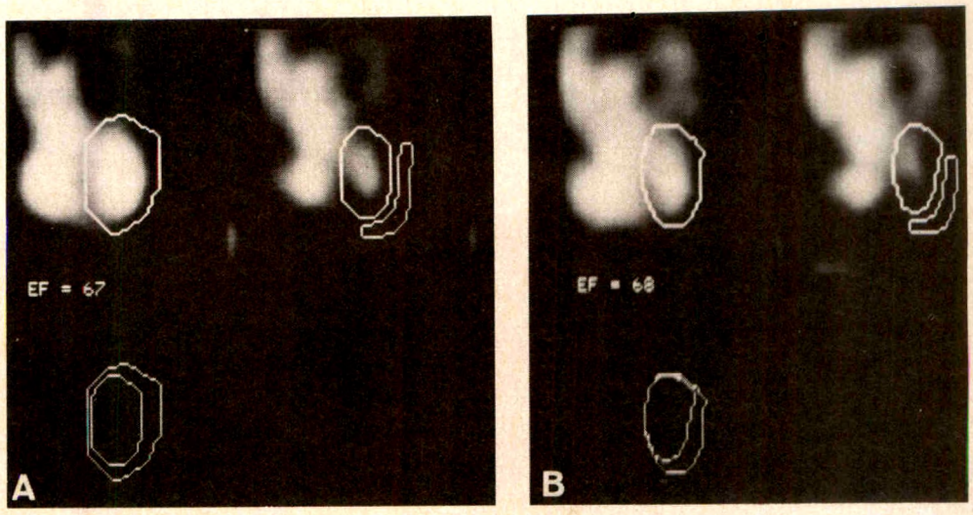

FIGURE 3. Case 5. Example of nuclear angiographic studies in a patient with no organic heart disease. **A,** baseline images; **B,** during paroxysmal supraventricular tachycardia. The end-diastolic frame (**upper left**), end-systolic frame and background region of interest (**upper right**), and superimposed end-diastolic and end-systolic regions of interest (**lower left**) are shown for each study. EF = ejection fraction (percent).

Ejection rate was comparable during tachycardia with and without atropine (4.2 versus 4.1). Normalized end-diastolic counts during tachycardia after atropine were greater than during tachycardia before atropine (36.4 versus 25.6 thousand counts) but still substantially decreased from the baseline value (59.9 thousand counts). Normalized stroke counts were decreased further during tachycardia after atropine (11.7 versus 14.5 thousand counts). Normalized count cardiac output was unchanged (2,499.3 versus 2,472.9 thousand counts).

Hemodynamics: Baseline Versus Post-Tachycardia (Table I)

Post-tachycardia studies were performed in 11 patients. However, one patient had received atropine for a second tachycardia study (see earlier) and therefore the post-tachycardia study in that patient did not represent a return to baseline condition. Thus 10 patients are included in the following analysis.

There was no statistically significant difference in heart rate or systolic or diastolic blood pressures in the baseline and post-tachycardia studies. This would be expected from the study design. In addition, there was no statistically significant difference in ejection fraction, ejection rate, end-diastolic counts, stroke counts or count cardiac output. Wall motion assessed in the post-tachycardia period was comparable with the baseline state in all patients.

Effect of Heart Disease and Rapid Heart Rate

Ejection fraction: Because only three patients had underlying organic heart disease and only two had a relatively rapid heart rate during tachycardia, we considered statistical analysis of these variables inappropriate. However, there were interesting features of the hemodynamic response to tachycardia in these five patients. Ejection fraction decreased by more than five percentage points during tachycardia in five patients. These were the three patients with organic heart disease (Cases 11, 12 and 13) and the two patients with the fastest heart rates during tachycardia (228 beats/min [Case 8] and 214 beats/min [Case 7, after atropine]). The decrease in ejection fraction in these five patients was 9, 15, 16, 14 and 10 percentage points, respectively. The third fastest heart rate during tachycardia was only 170 beats/min (Patient 7 before atropine) and was associated with an increase in ejection fraction over baseline (70 versus 65 percent). The three patients with organic heart disease had a marked decrease in ejection fraction during tachycardia despite a normal or borderline baseline ejection fraction (66, 54 and 53 percent, respectively).

TABLE II

Nuclear Angiographic Data Before and After Atropine in Patient 7

		Paroxysmal Supraventricular Tachycardia	
	Baseline	Before Atropine	After Atropine
Heart rate	73	170	214
Ejection fraction (%)	65	70	55
Ejection rate (mean ventricular counts/s)	2.7	4.1	4.2
End-diastolic counts ($\times 10^3$)	59.9	25.6	36.4
Stroke counts ($\times 10^3$)	30.8	14.5	11.7
Count cardiac output ($\times 10^3$)	2,247.7	2,472.9	2,499.3

Ejection rate and stroke volume: In addition, ejection rate decreased in only two patients during tachycardia (Cases 12 and 13). Both patients had organic heart disease. Stroke counts during tachycardia were decreased to less than 50 percent of the baseline value for five tachycardia studies in four patients. These were the patient (Case 8) with the fastest tachycardia (49 percent), the patient with the next fastest tachycardia (Case 7) both before and after atropine (47 and 38 percent, respectively) and two of the three patients (Cases 11 and 13) with organic heart disease (both 48

percent). The next two tachycardia studies with lowest stroke counts in relation to the baseline value were in one patient (Case 4) with neither a fast heart rate during tachycardia nor heart disease (52 percent) and in the third patient (Case 12) with organic heart disease (58 percent). It therefore appears that the presence of underlying organic heart disease or rapid heart rate during tachycardia greatly modified the hemodynamic response to tachycardia in the small number of patients studied.

Discussion

Previously reported studies: A number of reports[1–7] of single cases and small series have appeared concerning the effect of paroxysmal supraventricular tachycardia (often occurring fortuitously in the course of cardiac catheterization) on hemodynamic variables. In general, this tachycardia has been said to reduce blood pressure, stroke volume and cardiac output markedly. In addition, several investigators[3,4] noted large atrial waves in both the right atrial and pulmonary capillary wedge pressure tracings, most likely reflecting atrial systole against closed A-V valves. In one study,[4] a tendency was described for hemodynamic variables to be most abnormal at the onset of tachycardia and then to return gradually toward normal within the 1st minute of tachycardia. It should be noted that in the 14 patients reported on in the studies just cited,[1–7] the average heart rate during tachycardia was 187 beats/min. Most observations tended to be made very soon after the onset of tachycardia.

Two larger series of patients with hemodynamic measurements during paroxysmal supraventricular tachycardia have been reported.[8,9] Goldreyer et al.[8] studied eight patients with A-V nodal reentrant tachycardia who had reported disabling symptoms during tachycardia. The average heart rate during tachycardia was 183 beats/min. Tachycardia induced during cardiac catheterization was accompanied by a decrease in mean systolic arterial pressure from 141 to 99 mm Hg and a decrease in cardiac index from 3.6 to 2.2 liters/min per m^2. As in previous case reports, the observations of Goldreyer et al. were made early after the onset of tachycardia. Emphasis was placed on the first 60 to 90 seconds after induction of arrhythmia, and the observations of Sanders and Ord[4] of severe hemodynamic embarrassment at the onset of tachycardia were confirmed.

Schlepper et al.[9] reported hemodynamic observations during paroxysmal supraventricular tachycardia in 10 patients with a mean heart rate of 176 beats/min during tachycardia. Measurements were taken approximately every 2 minutes until tachycardia was terminated at 10 minutes. Expressed as a percent of baseline, mean aortic pressure varied from 68 percent at the onset of tachycardia to 92 percent in the 9th minute. Cardiac index ranged from 67 to 82 percent of baseline value and stroke volume from 36 to 41 percent. Measurements of maximal first derivative of left ventricular pressure (dP/dt) ranged from 60 percent of the baseline value at the onset of tachycardia to 107 percent in the 9th minute.

There is no previous study of hemodynamics during sustained arrhythmia using radionuclide studies. Measurement of ejection fraction and ejection rate and evaluation of wall motion by nuclear methods are well established procedures. Absolute ventricular volume measurements at rest and during exercise have also been described recently,[11,12] as have measurements of relative cardiac output under similar conditions.[17]

Methodology: In this study the patient served as his or her own control, and thus a relative method could be used for volume and output measurements. A prerequisite for this relative method is a normalization procedure. The one we used compensates for variable acquisition time, variable frame duration and radioactive decay. To minimize the errors in calculating stroke counts and count cardiac output, the end-diastolic region of interest alone was used so that stroke counts could be calculated without the need for background correction. This protocol allows comparison of baseline and tachycardia studies, even when tachycardia terminates spontaneously (as in Patients 7 and 10) before a preset number of counts is acquired.

Hemodynamic response to paroxysmal tachycardia: In our study, paroxysmal supraventricular tachycardia was characterized by a marked decrease in stroke volume. This finding is in agreement with previously reported results.[8,9] However, we found a modest increase in cardiac output (median value 132 percent of baseline) in contrast to the decrease reported previously. There are two possible reasons for this discrepancy. First, in most previous studies measurements were made early after the onset of tachycardia and reflect the more severely abnormal hemodynamics during this period. Second, the average heart rate during tachycardia in our study (157 beats/min) is somewhat slower than that of most previous studies. Of the two patients in the study by Goldreyer et al.[8] with a heart rate of less than 170 beats/min during tachycardia, one had a modest increase in cardiac index (4.1 to 4.3 liters/min per m^2) and the other had only a modest decrease (3.5 to 3.1 liters/min per m^2). The marked decrease in end-diastolic volume and the lack of change in ejection fraction and wall motion have not been previously described because these measurements would have necessitated performance of ventricular angiography during tachycardia.

Effect of very rapid heart rate and organic heart disease: In our study, a very rapid heart rate or the presence of underlying heart disease seemed to modify the hemodynamic response to paroxysmal supraventricular tachycardia. All three patients with organic heart disease and the two patients with the fastest heart rates during paroxysmal tachycardia had a marked decrease in ejection fraction. The decrease in stroke volume during tachycardia in relation to the baseline value also tended to be greatest in these patients. Although it is not surprising that the hemodynamic consequences of tachycardia should be more severe under these circumstances, it has not been demonstrated previously. Confirmation of these findings during tachycardia must await observations in larger groups of such patients. Ricci et al.[18] recently demonstrated a

decrease in ejection fraction during rapid atrial pacing in patients with heart disease.

Comparison with atrial pacing and exercise: Comparison of the hemodynamic consequences of paroxysmal supraventricular tachycardia with those of rapid heart rates achieved by atrial pacing and exercise may be instructive. Rushmer[19] reviewed previous data showing that stroke volume changed very little during exercise in dogs and human beings. He confirmed this observation in 37 dogs and compared the response to rapid atrial pacing by driving an atrial pacemaker at the dog's tape-recorded heart rate during exercise. During pacing, end-diastolic diameter and stroke volume decreased greatly. Since Rushmer's report, several studies[20–23] have confirmed maintenance of end-diastolic dimensions with little change or even an increase in stroke volume during exercise. These events result in a large increase in cardiac output. Using nuclear angiography, Slutsky et al.[12] observed an increase in ejection fraction during exercise from 67 to 80 percent with no significant change in end-diastolic volume (15.8 versus 15.2 volume units), implying an increase in stroke volume. Sorensen et al.[17] observed that count cardiac output increased an average of almost 400 percent during exercise in nine normal men.

In contrast, rapid atrial pacing consistently caused a decrease in end-diastolic volume and stroke volume with little if any resulting change in cardiac output.[19,24–30] There has been as yet no study of the hemodynamics of rapid atrial pacing using nuclear angiography. Wisenberg et al.[31] reported little change in ejection fraction or cardiac output (+4 percent), with decreases in end-diastolic (−29 percent) and stroke (−37 percent) volumes at heart rates of up to 100 beats/min. It is clear, then, that the hemodynamic features of paroxysmal supraventricular tachycardia are similar to those of rapid atrial pacing and not those of exercise.

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Paroxysmal Atrial Fibrillation in the Wolff-Parkinson-White Syndrome

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Eighty-eight patients with preexcitation were studied to determine how 30 patients with documented spontaneous paroxysmal atrial fibrillation differed from 58 patients without this arrhythmia. Inducible reentrant tachycardia was present in 23 (77 percent) of the 30 patients with, versus 28 (48 percent) of the 58 patients without, atrial fibrillation ($p < 0.025$). Heart disease was present in 13 (43 percent) of the 30 patients with, versus 15 (26 percent) of the 58 patients without, atrial fibrillation (not significant). Inducible reentrant tachycardia or heart disease, or both, were present in 29 (97 percent) of the 30 patients with, versus 34 (59 percent) of the 58 patients without, atrial fibrillation ($p < 0.0005$).

Of 51 patients with inducible reentrant tachycardia, 23 patients with atrial fibrillation did not differ from 28 patients without this arrhythmia with respect to clinical features and atrial, sinus nodal, or anomalous pathway properties, or cycle length of induced reentrant tachycardia. Spontaneous degeneration of induced reentrant tachycardia to atrial fibrillation was observed in 6 (26 percent) of 23 patients with, versus none of 28 patients without, atrial fibrillation ($p < 0.025$).

In summary, patients with preexcitation and documented spontaneous paroxysmal atrial fibrillation almost always have inducible reentrant tachycardia or heart disease, or both. It is likely that in many patients with inducible reentrant tachycardia, spontaneously occurring reentrant tachycardia relates to induction of atrial fibrillation. However, it is unclear why some patients with inducible reentrant tachycardia have atrial fibrillation and others do not. In many patients with organic heart disease, atrial fibrillation could relate to hemodynamic changes.

Some patients with preexcitation have recurrent paroxysmal supraventricular tachycardia or paroxysmal atrial fibrillation, or both.[1–4] The former arrhythmia usually reflects the occurrence of atrioventricular (A-V) reentrance, utilizing normal and anomalous A-V pathways.[5–8] Induction of A-V reentrant paroxysmal tachycardia reflects the presence of measurable normal and anomalous pathway properties.[8] In contrast, the pathophysiology of paroxysmal atrial fibrillation in patients with preexcitation is less clear. Several groups of investigators[9–11] have suggested that in some patients with preexcitation, paroxysmal atrial fibrillation might result from A-V reentrant tachycardia.

In this study, we attempted to elucidate further the pathophysiology of paroxysmal atrial fibrillation in preexcitation, by attempting to measure clinical and electrophysiologic variables, in a series of 88 patients with preexcitation. We attempted to determine how patients with preexcitation who have documented episodes of spontaneous paroxysmal atrial fibrillation differ from those without this arrhythmia.

Methods

Patient selection: Criteria for inclusion in the study were: (1) evidence of typical preexcitation in one or more electrocardiograms during normal sinus rhythm, and (2) referral to our laboratory for cardiac electrophysiologic studies (see later). Both symptomatic and asymptomatic patients were studied with use of a protocol approved by our institutional human investigation committee.

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Eighty-eight patients referred to our institution between December 1972 and February 1980 fulfilled these criteria. Sixty-seven were male and 21 female; their ages ranged from 12 to 67 years (mean ± standard deviation 36 ± 15). Thirty of the 88 patients had had one or more electrocardiographically documented episodes of spontaneous paroxysmal atrial fibrillation, the other 58 patients had not had documented atrial fibrillation. Nineteen of the 88 patients had intermittent preexcitation (one or more electrocardiograms failed to show preexcitation during normal sinus rhythm).

Clinical evaluation: Electrocardiograms of documented arrhythmias were obtained from referring physicians and hospital emergency rooms. Atrial fibrillation and paroxysmal supraventricular tachycardia were diagnosed using standard electrocardiographic criteria.[12] The presence or absence of organic heart disease was determined by history, physical examination, electrocardiogram, chest roentgenogram and (after July 1974) echocardiogram. Diagnostic cardiac catheterization was performed when clinically indicated. Standard criteria were used to diagnose and classify organic heart disease.[13]

Electrophysiologic studies: These studies were performed in the postabsorptive, nonsedated state after cardioactive drugs had been discontinued for at least 48 hours. Informed written consent was obtained from all patients. The electrophysiologic protocol performed has previously been reported[4] and included the following: (1) recording of basic conduction intervals during regular sinus rhythm; (2) incremental pacing from several atrial sites; (3) atrial extrastimulus testing during sinus rhythm and at an atrial paced cycle length of 600 ms; (4) incremental ventricular pacing; and (5) ventricular extrastimulus testing. No systematic attempt was made to induce atrial fibrillation in this series of patients.

Patients were assessed for ability to have induced A-V reentrant tachycardia, in which the normal conduction system is utilized for anterograde conduction and the anomalous pathway is utilized for retrograde conduction (orthodromic variety),[7,8] or in which the anomalous pathway is utilized for anterograde conduction and the normal pathway is utilized for retrograde conduction (antedromic variety).[14–16] Criteria employed by us and others for diagnosis of these varieties of paroxysmal tachycardia have also been reported elsewhere.[4,16] Patients were considered to have inducible A-V reentrant tachycardia when one or more modalities of cardiac stimulation (see earlier) resulted in A-V reentrant tachycardia that was sustained for 2 or more minutes (in the absence of atropine or isoproterenol).

In the patients who had inducible tachycardia, the following were noted: (1) cycle length of induced tachycardia; (2) the effect (or lack of effect) of occurrence of functional bundle branch block on cycle length of induced tachycardia[17,18]; (3) atrial activation sequence during induced tachycardia (determined by recording from multiple atrial sites)[7,19,20]; and (4) occurrence of spontaneous (not associated with cardiac stimulation) conversion of induced tachycardia to atrial fibrillation.[10,11] Patients were considered not to have inducible A-V reentrant tachycardia when all modalities of cardiac stimulation failed to produce A-V reentrant echo beats or produced only single echo beats or brief episodes of self-terminating tachycardia.

Anomalous pathway location was determined by application of combinations of the following observations: (1) QRS configuration during regular sinus rhythm[21]; (2) QRS configuration during maximal preexcitation (obtained by pacing the atria at rates faster than sinus heart rate)[21]; (3) the atrial pacing site that resulted in the shortest stimulus-delta wave interval[22]; (4) atrial activation sequence during ventricular pacing and induced A-V reentrant tachycardia[7,19,20]; and (5) the effect (or lack of effect) of functional bundle branch block on cycle length of induced A-V reentrant tachycardia.[17,18]

Corrected sinus nodal recovery time[23] *and calculated sinoatrial conduction time*[24] *were defined and measured as previously described.* High right atrial refractory periods were determined at a paced cycle length (A_1-A_1) of 600 ms. The atrial functional refractory period was defined as the shortest A_1-A_2 interval achieved. The atrial effective refractory period was defined as the longest S_1-S_2 interval at which the extrastimulus (S_2) failed to produce an atrial response (A_2). Dispersion of atrial effective refractory period was defined as the difference between atrial effective refractory periods measured in the high right atrium and in the coronary sinus at a paced cycle length of 600 ms.[25]

Statistical analyses: Comparisons between the two groups of patients with respect to the presence or absence of specific attributes were made by 2 by 2 chi-square analysis with Yates' correction. Comparisons between the two groups of patients with respect to anomalous pathway location were made by 3 by 2 chi-square analysis. Comparisons between the two groups of patients with respect to numerical data were made by *t* test for unpaired data.

Results

Characteristics of study group: Thirty (34 percent) of the 88 study patients had electrocardiographically documented episodes of spontaneous paroxysmal atrial fibrillation before referral (12 patients had had one episode, and 18 patients had had two or more episodes). Mean ventricular rates during atrial fibrillation in these patients ranged from 130 to 300 beats/min (mean ± standard deviation, 204 ± 44), and the shortest R-R intervals ranged from 150 to 410 ms (223 ± 68). Twenty-one of these patients had required direct current cardioversion on one or more occasions. The other 58 (66 percent) of the 88 study patients did not have documented atrial fibrillation.

Before referral, 33 (38 percent) of the 88 study patients had electrocardiographically documented episodes of spontaneous paroxysmal supraventricular tachycardia, whereas 55 (62 percent) did not. During electrophysiologic studies, 51 (58 percent) of the 88 study patients had inducible A-V reentrant tachycardia (orthodromic variety in 49 patients and antedromic variety in 2 patients), whereas 37 (42 percent) did not. Twenty-eight (32 percent) of the 88 patients had organic heart disease (Table I), whereas 60 (68 percent) did not.

Comparisons of patients with and without spontaneous paroxysmal atrial fibrillation: We attempted to determine how the 30 patients with documented spontaneous paroxysmal atrial fibrillation differed from the 58 patients without documented atrial fibrillation. The two groups did not differ with respect to age: The mean age of each group was 36 years. The groups also did not differ significantly with respect to sex: Twenty-five (83 percent) of the 30 patients with documented atrial fibrillation and 42 (72 percent) of the 58 patients without atrial fibrillation were male. Of the 30 patients with documented atrial fibrillation, 9 (30 percent) had left free wall, 15 (50 percent) had septal or paraseptal and 6 (20 percent) had right free wall anomalous pathways, whereas of the 58 patients without atrial fibrillation, 17 (29 percent) had left free wall, 18

TABLE I

Associated Heart Disease in 88 Patients with Wolff-Parkinson-White Syndrome

	Patients With Atrial Fibrillation (30 patients)	Patients Without Atrial Fibrillation (58 patients)
Coronary artery disease	1	2
Hypertensive heart disease	1	5
Cardiomyopathy	5	3
Valvular heart disease	4	2
Cor pulmonale	0	1
Congenital heart disease		
Ebstein's anomaly	2	0
Atrial septal defect	0	1
Corrected transposition	0	1
Total	13	15

(31 percent) had septal or paraseptal, and 23 (40 percent) had right free wall anomalous pathways (difference not significant [NS]).

Relation of paroxysmal atrial fibrillation to spontaneous and inducible paroxysmal tachycardia and to organic heart disease (Table II): We attempted to determine whether the 30 patients with documented episodes of spontaneous paroxysmal atrial fibrillation differed from the 58 patients without documented atrial fibrillation with respect to the occurrence of spontaneous paroxysmal supraventricular tachycardia, the presence of inducible A-V reentrant tachycardia or the presence of organic heart disease. Before referral, 9 (30 percent) of the 30 patients with and 24 (41 percent) of the 58 patients without atrial fibrillation had documented episodes of spontaneous paroxysmal supraventricular tachycardia (NS). During electrophysiologic study, 23 (77 percent) of the 30 patients with documented atrial fibrillation and 28 (48 percent) of the 58 patients without atrial fibrillation had inducible A-V reentrant tachycardia (Fig. 1). The patients with documented atrial fibrillation were significantly more likely to have inducible A-V reentrant tachycardia than were the patients without atrial fibrillation ($p < 0.025$).

TABLE II

Comparisons of Patients With and Without Spontaneous Paroxysmal Atrial Fibrillation

	Patients With Atrial Fibrillation (30 patients)	Patients Without Atrial Fibrillation (58 patients)	p Value
Spontaneous PSVT	9 (30%)	24 (41%)	NS
Inducible PSVT	23 (77%)	28 (48%)	<0.025
Organic heart disease	13 (43%)	15 (26%)	NS
Organic heart disease in 37 patients without inducible PSVT	6 of 7 (86%)	6 of 30 (20%)	<0.005
Organic heart disease or inducible PSVT, or both	29 (97%)	34 (59%)	<0.0005

PSVT = atrioventricular reentrant paroxysmal tachycardia.

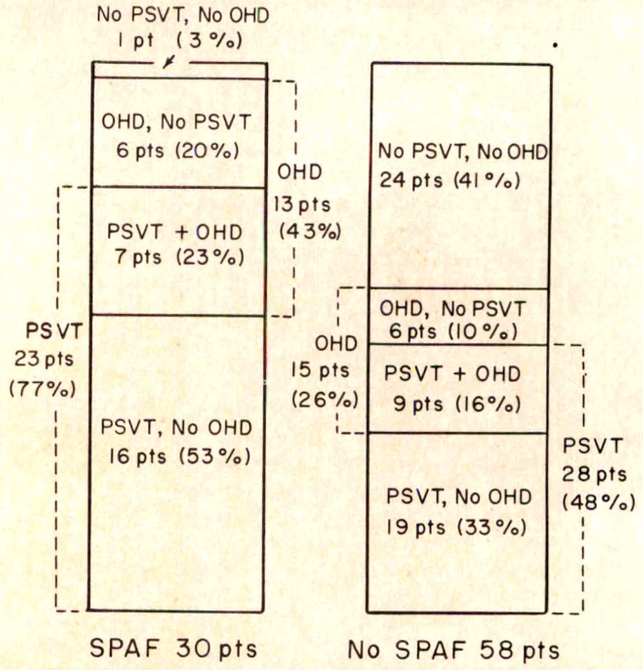

FIGURE 1. Association of spontaneous paroxysmal atrial fibrillation (SPAF) with inducible A-V reentrant tachycardia (PSVT) or organic heart disease (OHD), or both. The 30 patients (pts) with documented episodes of atrial fibrillation are shown on the **left**, and the 58 patients without such episodes are shown on the **right**. See text for discussion.

Thirteen (43 percent) of the 30 patients with documented atrial fibrillation and 15 (26 percent) of the 58 patients without atrial fibrillation had organic heart disease (Table I, Fig. 1). These prevalence levels were not significantly different. However, six (86 percent) of the seven patients with documented atrial fibrillation who did not have inducible A-V reentrant paroxysmal tachycardia had organic heart disease (Fig. 1). In contrast, only 6 (20 percent) of the 30 patients without atrial fibrillation who did not have inducible A-V reentrant tachycardia had organic heart disease ($p < 0.005$) (Fig. 1). Viewed in another way, 29 (97 percent) of the 30 patients with documented atrial fibrillation had inducible A-V reentrant tachycardia or organic heart disease, or both. In contrast, only 34 (59 percent) of the 58 patients without atrial fibrillation had inducible A-V reentrant tachycardia or organic heart disease, or both ($p < 0.0005$).

Inducible A-V reentrant tachycardia in patients with and without spontaneous paroxysmal atrial fibrillation: The finding that patients with documented atrial fibrillation were significantly more likely to have inducible A-V reentrant tachycardia than patients without atrial fibrillation suggested that there is an association between spontaneous paroxysmal atrial fibrillation and inducible A-V reentrant tachycardia. Of the 51 patients with inducible A-V reentrant tachycardia, 23 had documented atrial fibrillation whereas 28 did not. We further scrutinized the patients with inducible A-V reentrant tachycardia, to determine

whether the patients with documented atrial fibrillation differed from the patients without atrial fibrillation with respect to clinical and electrophysiological characteristics.

There were no apparent differences between these two groups of patients with inducible A-V reentrant tachycardia with respect to clinical characteristics. Ages ranged from 15 to 61 years (mean ± standard error of the mean, 34 ± 3) among patients with documented atrial fibrillation, and from 12 to 64 years (mean 35 ± 3) among patients without atrial fibrillation (NS). Nineteen (83 percent) of the 23 patients with documented atrial fibrillation and 17 (61 percent) of the 28 patients without atrial fibrillation were male (NS). Seven (30 percent) of the 23 patients with documented atrial fibrillation and 9 (32 percent) of the 28 patients without atrial fibrillation had organic heart disease (NS) (Fig. 1).

We next compared sinus nodal and atrial properties in these two groups of patients with inducible A-V reentrant tachycardia. Corrected sinus nodal recovery times ranged from 120 to 470 ms (mean 295 ± 19) in the 23 patients with documented atrial fibrillation and from 124 to 490 ms (mean 307 ± 21) in the 28 patients without atrial fibrillation (NS). Calculated sinoatrial conduction times ranged from 20 to 125 ms (mean 75 ± 6) in the patients with documented atrial fibrillation and from 25 to 142 ms (mean 90 ± 7) in the patients without atrial fibrillation (NS). Atrial functional refractory periods ranged from 200 to 330 ms (mean 261 ± 12) in the patients with documented atrial fibrillation and from 200 to 350 ms (mean 254 ± 6) in the patients without atrial fibrillation (NS). Atrial effective refractory periods ranged from 160 to 290 ms (mean 225 ± 8) in the patients with documented atrial fibrillation, and from 140 to 330 ms (mean 207 ± 7) in the patients without atrial fibrillation (NS). Dispersion of atrial effective refractory periods (between high right atrium and coronary sinus) ranged from 10 to 70 ms (mean 30 ± 10) in seven patients with documented atrial fibrillation and from 10 to 50 ms (mean 24 ± 7) in five patients without atrial fibrillation (NS).

We also examined characteristics of the induced tachycardias in these two groups of patients with inducible A-V reentrant tachycardia. Cycle lengths of induced A-V reentrant tachycardia ranged from 250 to 375 ms (mean 320 ± 8) in the patients with documented atrial fibrillation and from 260 to 440 ms (mean 319 ± 9) in the patients without atrial fibrillation (NS) (Fig. 2). The location of the anomalous pathway (the site of input to the atria during the orthodromic variety of A-V reentrant tachycardia) was the left ventricular free wall in 9 (39 percent), septal or paraseptal wall in 10 (43 percent) and the right free wall in 4 (17 percent) of the 23 patients with documented atrial fibrillation; the site was the left free wall in 13 (46 percent), septal or paraseptal wall in 5 (18 percent) and the right free wall in 10 (36 percent) of the 28 patients without atrial fibrillation (NS). One (4 percent) of the 23 patients with and 2 (7 percent) of the 28 patients without atrial fibrillation had a second anomalous pathway,[26] which could possibly

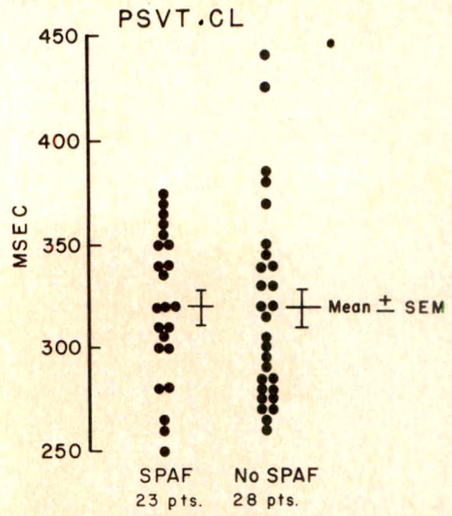

FIGURE 2. Cycle lengths (CL) of induced A-V reentrant tachycardia (PSVT). The cycle lengths did not differ in patients (**left**) with and without (**right**) documented spontaneous paroxysmal atrial fibrillation (SPAF).

allow two inputs to the atria during A-V reentrant tachycardia (NS). Induced tachycardias were different in these two groups of patients in one respect: Induced A-V reentrant tachycardia was observed to degenerate spontaneously to atrial fibrillation in 6 (26 percent) of the 23 patients with documented episodes of spontaneous paroxysmal atrial fibrillation (Fig. 3) but in none of the 28 patients without such episodes ($p < 0.025$).

In summary, the only significant difference between the patients with inducible A-V reentrant tachycardia who did and did not have documented episodes of spontaneous paroxysmal atrial fibrillation was that spontaneous degeneration of induced A-V reentrant tachycardia to atrial fibrillation was observed exclusively in the former group.

Organic heart disease in patients without inducible A-V reentrant tachycardia: We also studied the 37 patients without inducible A-V reentrant tachycardia in an attempt to determine how the 7 patients with documented atrial fibrillation differed from the 30 patients without atrial fibrillation. We found that organic heart disease was more commonly present among the patients with than among those without atrial fibrillation (see earlier) (Fig. 1).

Six (86 percent) of the seven patients with documented atrial fibrillation had organic heart disease. Four of these patients had heart disease that was hemodynamically significant: Three had congestive cardiomyopathy and one had calcific mitral stenosis (calculated mitral valve area 1.3 cm^2). Of the remaining two patients with heart disease, one had clinical, echocardiographic and angiographic evidence of mitral valve prolapse, and one had the echocardiographic finding of asymmetric septal hypertrophy (interventricular septum to left ventricular posterior wall thickness ratio of 1.8) but no resting or provokable left ventricular outflow tract obstruction. Therefore, among these seven pa-

tients without inducible A-V reentrant tachycardia, the occurrence of spontaneous paroxysmal atrial fibrillation probably was related to organic heart disease in four (atrial stretch), and possibly in two other patients.

Six (20 percent) of the 30 patients without documented atrial fibrillation had organic heart disease. Three of these patients had heart disease that was hemodynamically significant: One had congestive cardiomyopathy, one had a previous myocardial infarction and congestive failure, and one had hypertensive heart disease with cardiomegaly. Of the remaining three patients with heart disease, one had angina pectoris, one had mild hypertensive heart disease and one had an ostium secundum atrial septal defect (with a pulmonary to systemic blood flow ratio of 2.0).

Discussion

Some patients with preexcitation have recurrent paroxysmal supraventricular tachycardia or paroxysmal atrial fibrillation or both.[1–4] The former usually reflects the occurrence of A-V reentrance, in which an impulse conducts from the atria in anterograde manner over the normal pathway (A-V node and His-Purkinje system) to the ventricles, and then in retrograde manner over the anomalous pathway (Kent bundle) to the atria.[5–8] Induction of this variety of paroxysmal tachycardia requires the presence of specific measurable cardiac electrophysiologic properties, namely, the ability of the normal pathway to conduct sequential impulses in an anterograde direction and the ability of the anomalous pathway to conduct sequential impulses in a retrograde direction.[8] In contrast, the pathophysiology of paroxysmal atrial fibrillation in patients with preexcitation is less clear.

Several groups of investigators have suggested that, in some patients with preexcitation, initiation of paroxysmal atrial fibrillation could relate to the occurrence of A-V reentrant tachycardia.[9–11] While performing

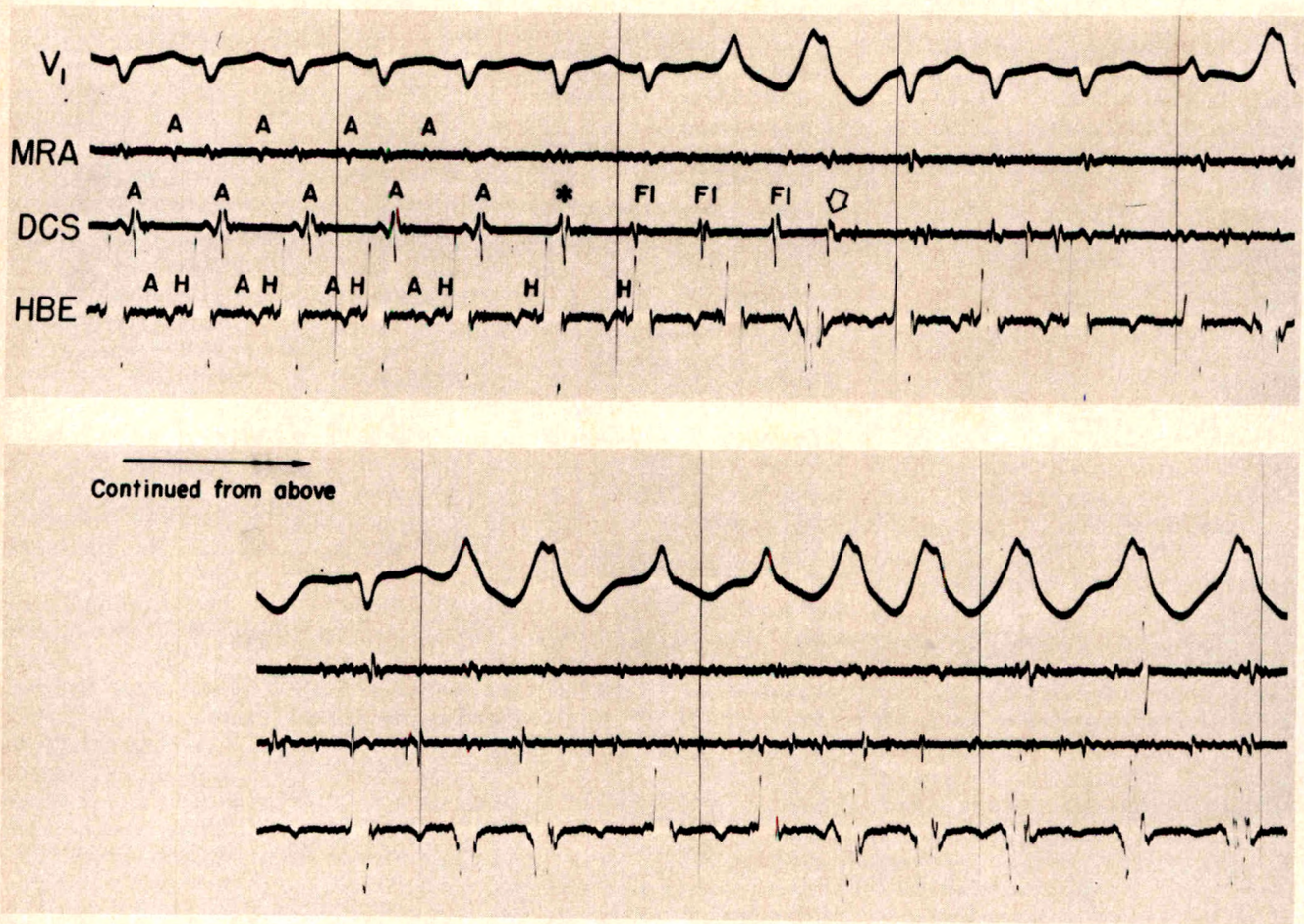

FIGURE 3. Continuous recording showing spontaneous degeneration of induced A-V reentrant tachycardia to atrial fibrillation. Shown are electrocardiographic lead V_1 and mid right atrial (MRA), distal coronary sinus (DCS), and His bundle (HBE) electrograms. Time lines are at 1 s intervals. The first several beats (**top panel, left**) reflect A-V reentrant tachycardia (notice that coronary sinus electrogramsprecede right atrial electrograms). The sixth coronary sinus deflection (**asterisk**) is premature, and is followed by several beats of atrial flutter (FI). The **arrow** marks the approximate onset of atrial fibrillation (notice the subsequent fragmentation and irregularity of atrial electrograms). After the onset of atrial fibrillation, several beats are normally conducted before the typical features of atrial fibrillation with anterograde conduction over an anomalous pathway are established (**lower panel**).

cardiac electrophysiologic studies in patients with preexcitation, these investigators observed degeneration of induced A-V reentrant tachycardia to atrial fibrillation. Campbell et al.[10] reported on 10 patients whose atrial fibrillation resulted from spontaneous (not related to cardiac pacing) degeneration of induced A-V reentrant tachycardia, and an additional 6 patients in whom atrial fibrillation resulted from atrial or ventricular stimulation during induced tachycardia or from ventricular pacing alone. The spontaneous degenerations appeared to relate to the occurrence of either premature atrial beats or intraatrial conduction delay during induced A-V reentrant tachycardia. Sung et al.[11] reported on seven patients in whom spontaneous degeneration of induced tachycardia appeared to relate to the occurrence of premature atrial beats. Both Sung and Campbell and their co-workers took care to exclude from their reports patients in whom degeneration occurred during catheter manipulation. However, neither report clearly established the relevance of these laboratory observations to the occurrence of spontaneous paroxysmal atrial fibrillation. Only 6 of the 16 patients reported on by Campbell et al. and 5 of the 7 patients reported on by Sung et al. had documented episodes of atrial fibrillation before the electrophysiologic study was performed.

Association between presence of spontaneous fibrillation and inducible A-V reentrant tachycardia: In the present study, we studied a series of 88 patients with preexcitation in an attempt to determine how the 30 patients who had had electrocardiographically documented episodes of spontaneous paroxysmal atrial fibrillation differed from the 58 patients without documented atrial fibrillation. The patients with documented atrial fibrillation were significantly more likely to have inducible A-V reentrant tachycardia than were the patients without documented atrial fibrillation. In other words, there was a significant association between the presence of documented atrial fibrillation (a clinical event) and the presence of inducible A-V reentrant tachycardia (a laboratory event). The significance of this association merits further discussion.

In a previous study of patients with preexcitation, we[4] noted that the presence or absence of inducible A-V reentrant tachycardia correlated strongly with the clinical occurrence of paroxysmal supraventricular tachycardia. For example, we found that the large majority of patients with inducible A-V reentrant tachycardia had had documented episodes of paroxysmal supraventricular tachycardia or paroxysmal palpitation without documented arrhythmia (suspected A-V reentrant tachycardia). In the present study, we noted that, although 77 percent of our patients with documented atrial fibrillation had inducible A-V reentrant tachycardia, only 30 percent of these patients had had documented episodes of paroxysmal supraventricular tachycardia. It is likely that many of our patients with preexcitation and documented atrial fibrillation had episodes of A-V reentrant tachycardia that degenerated to atrial fibrillation; (therefore it was atrial fibrillation rather than A-V reentrant tachycardia that was documented electrocardiographically). This hypothesis is supported by recent observations in two of our patients with preexcitation (one reported on).[27] These two patients, referred to us because of recurrent episodes of paroxysmal atrial fibrillation, had not had documented episodes of paroxysmal supraventricular tachycardia but were found to have inducible A-V reentrant tachycardia. After electrophysiologic studies, these patients were issued transmitters, enabling them to report by telephone future cardiac rhythms disturbances. Their rhythm during the first minutes of subsequent episodes of paroxysmal palpitation was paroxysmal supraventricular tachycardia (telephone transmissions), but later during these episodes (on arrival in emergency room) the rhythm was atrial fibrillation.

Differences between patients with A-V reentrant tachycardia with and without atrial fibrillation: If one accepts the hypothesis that spontaneous paroxysmal atrial fibrillation is sometimes (or frequently) the result of paroxysmal A-V reentrant tachycardia, then it is germane to ask why some patients with preexcitation and A-V reentrant tachycardia have atrial fibrillation and others do not. We attempted to answer this question by further studying our patients who had inducible A-V reentrant tachycardia and comparing the patients with and without documented atrial fibrillation. These two groups of patients did not differ with respect to clinical attributes (age, sex or the presence of organic heart disease) or atrial properties (including dispersion of effective refractory period between high right atrium and coronary sinus). Because Dreifus et al.[28] suggested that paroxysmal atrial fibrillation in patients with preexcitation may be associated with sinus nodal dysfunction, we also examined sinus nodal properties. However, our patients with and without documented atrial fibrillation did not differ with respect to corrected sinus nodal recovery time or calculated sinoatrial conduction time.

Wyndham[29] and Sung[11] and their co-workers reported that atrial vulnerability in human beings increases as atrial cycle length decreases. We therefore hypothesized that in patients with preexcitation who have spontaneous episodes of paroxysmal atrial fibrillation A-V reentrant tachycardia may be faster than in patients without such episodes. However, we found that our patients with and without documented atrial fibrillation had induced A-V reentrant tachycardias of almost identical cycle lengths. We also found that neither anomalous pathway location (the site of input to the atria during A-V reentrant tachycardia) nor the prevalence of two anomalous pathways (possibly allowing two inputs to the atria during A-V reentrant tachycardia) differed in patients with and without documented atrial fibrillation. These two groups of patients differed in only one respect: Spontaneous degeneration of induced A-V reentrant tachycardia to atrial fibrillation was observed significantly more often in the patients who had documented atrial fibrillation. In other words, the only distinguishing characteristic of the patients with inducible A-V reentrant tachycardia

who had documented atrial fibrillation was that they had (in the laboratory) the hypothesized event itself.

There are several possible explanations for why some patients with preexcitation and A-V reentrant tachycardia have paroxysmal atrial fibrillation and others do not. (1) There could be differences in dispersion of atrial refractoriness on a microscopic scale (rather than on a macroscopic scale, as measured in the present study).[25] (2) There could be differences in hemodynamic responses to A-V reentrant tachycardia (hemodynamic variables were not measured in the present study).[30,31] (3) There could be differences in autonomic responses (perhaps related to hemodynamic responses) to A-V reentrant tachycardia; for example, an increase in parasympathetic nervous tone during A-V reentrant tachycardia could predispose to the occurrence of paroxysmal atrial fibrillation.[32,33]

Role of organic heart disease: It is reasonable to assume that patients with preexcitation and significant underlying organic heart disease are predisposed to the occurrence of paroxysmal atrial fibrillation. However, it appears that only a minority of patients with preexcitation and paroxysmal atrial fibrillation have heart disease. Wellens[9] diagnosed heart disease in 9 of 27 patients, whereas Campbell et al.[10] found heart disease in 6 of 32 patients with paroxysmal atrial fibrillation. In the present study, we found organic heart disease (of several different varieties) in 13 (43 percent) of our patients with preexcitation and documented episodes of spontaneous paroxysmal atrial fibrillation. Similar to Campbell et al.[10] we did not find a greater prevalence of organic heart disease in patients with than in patients without paroxysmal atrial fibrillation.

If one accepts the hypothesis that patients with preexcitation who have A-V reentrant tachycardia are predisposed to the occurrence of paroxysmal atrial fibrillation, then it is reasonable to ask why some patients with preexcitation who do not have A-V reentrant tachycardia have paroxysmal atrial fibrillation. When we limited our analysis to patients who did not have inducible A-V reentrant tachycardia, we found that patients with documented atrial fibrillation had a much greater prevalence of organic heart disease than did patients without documented atrial fibrillation. In fact, six (83 percent) of the seven patients with documented atrial fibrillation who did not have inducible A-V reentrant tachycardia had organic heart disease. In four of these six patients, organic heart disease was clearly hemodynamically significant (three had congestive cardiomyopathy and one had significant mitral stenosis) and in all probability was related to the occurrence of paroxysmal atrial fibrillation. In the other two patients, organic heart disease was not hemodynamically significant and may or may not have been related to the occurrence of paroxysmal atrial fibrillation.

Therapeutic implications: The usual approach to long-term management (prophylaxis) of the patient with preexcitation and recurrent atrial fibrillation is to administer one or more drugs that increase the anterograde refractoriness of the anomalous pathway,[34–39] or to divide surgically the anomalous pathway[40] to prevent rapid ventricular rates during recurrences of atrial fibrillation. A different approach would be to administer drugs in an attempt to actually prevent recurrences of atrial fibrillation. However, this latter approach is poorly understood, and clinical trial and error is currently the only method available for evaluating drug responses. In contrast, there is far more understanding of pharmacologic prophylaxis of A-V reentrant tachycardia,[34–39,41–44] and serial drug testing can be performed in the catheterization laboratory,[43] eliminating the need for extensive clinical trial and error.

The demonstration in this study that patients with preexcitation and spontaneous paroxysmal atrial fibrillation usually have inducible A-V reentrant tachycardia implies that administration of drugs to these patients to prevent paroxysmal supraventricular tachycardia could also prevent recurrences of atrial fibrillation. It also implies that surgical division of the anomalous pathway (the retrograde limb of A-V reentrant tachycardia) could also prevent recurrences of atrial fibrillation.

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Echocardiographic Abnormalities in Chronic Alcoholics With and Without Overt Congestive Heart Failure

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To assess the type and prevalence of cardiac abnormalities in heavy drinkers with and without overt congestive heart failure, M mode echocardiography was performed in 11 symptomatic chronic alcoholics with dilated (congestive) cardiomyopathy and in 22 asymptomatic chronic alcoholics. Echocardiographic data in both groups were adjusted for age and body surface area using previously derived regression equations. All 11 symptomatic patients had a significantly decreased left ventricular percent fractional shortening (mean 14 percent, normal range 28 to 44) along with significant increases in left ventricular systolic and diastolic dimensions (mean increases of 105 and 48 percent above normal, respectively), left atrial dimension (mean increase 21 percent) and estimated left ventricular mass (mean increase 105 percent). Among the 22 asymptomatic patients, 15 (68 percent) demonstrated significant increases in at least one of the following echocardiographic variables: left ventricular mass, left ventricular dimensions, septal and left ventricular wall thicknesses, and left atrial dimension.

Asymptomatic patients could be classified into two subgroups: (1) those with a left ventricular diastolic dimension less than 10 percent above the normal predicted value and an increased left ventricular wall thickness to radius ratio (mean increase 16 percent above normal) and upper normal percent fractional shortening, and (2) those with a left ventricular diastolic dimension 10 to 24 percent above normal and a slightly subnormal thickness to radius ratio and lower normal percent fractional shortening. Echocardiographic abnormalities in asymptomatic chronic alcoholics did not correlate with the presence or absence of auscultatory abnormalities on physical examination and appear to reflect an earlier stage in the spectrum of alcoholic disease before the development of dilated cardiomyopathy.

One of the complications of chronic alcoholism is the development of dilated (congestive) cardiomyopathy. Despite some controversy as to its etiologic role in cardiomyopathy, ethanol has been incriminated in the production of left ventricular failure by a direct cardiotoxic effect.[1–4] The hemodynamic features of the disease at this stage reflect depression of myocardial contractile function and include ventricular dilatation, decreased left ventricular ejection fraction and increased end-diastolic pressure in both ventricles. Left ventricular angiography has also demonstrated an increase in left ventricular wall thickness and overall myocardial mass.[5] Previous echocardiographic studies[6,7] of dilated cardiomyopathy have shown increased left ventricular diastolic and systolic dimensions, markedly decreased ventricular septal and posterior left ventricular wall motion, and a decrease in left ventricular percent fractional shortening and mean velocity of circumferential fiber shortening.

Evidence of cardiac malfunction has also been demonstrated in chronic alcoholics without clinical evidence of heart disease both invasively[8,9] and by noninvasive measurement of systolic time inter-

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TABLE I

Symptomatic Chronic Alcoholics: Clinical and Echocardiographic Characteristics

Case	Age (yr)	BP	FC	Aus	BSA (cm^2)	LVIDd (mm)	LVIDs (mm)	VST (mm)	LVWT (mm)	ARD (mm)	LAD (mm)	LV % FS	LV Mass (g)	t/r
1	43	110/70	III	S_3, S_4	1.70	58	49	8	10	28	34	16	256	0.31
2	41	110/70	IV	S_3, S_4	1.83	76	71	10	10	28	?	7	468	0.26
3	53	154/80	III	S_3, S_4	2.09	72	61	14	14	33	48	15	658	0.39
4	60	120/70	II	S_3, S_4	1.67	73	66	13	12	28	46	10	580	0.34
5	62	104/80	II	S_3, S_4	1.81	68	60	9	10	28	52	12	361	0.28
6	66	95/60	IV	S_3, S_4	1.66	73	59	11	12	30	52	19	521	0.31
7	28	110/70	II	S_3, S_4	1.92	75	69	12	13	32	44	8	607	0.33
8	50	118/70	II	S_3, S_4	1.88	60	50	11	12	32	38	17	374	0.38
9	51	115/85	III	S_3, S_4	2.07	78	71	12	11	38	38	9	584	0.29
10	63	125/60	IV	S_3, S_4	1.90	66	50	13	13	34	52	24	516	0.39
11	55	120/87	II	S_3, S_4	2.00	79	67	10	10	32	42	15	501	0.25
Mean	52	. . .	. . .	. . .	1.87	71	61	11	11.5	31	45	14	493	0.32

ARD = aortic root dimension; Aus = auscultation; BP = blood pressure; BSA = body surface area; FC = New York Heart Association functional class; LAD = left atrial dimension; LV = left ventricular; LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; LVWT = left ventricular diastolic wall thickness; % FS = percent fractional shortening; t = average left ventricular diastolic thickness, or (LVWT + VST)/2; t/r = thickness to radius ratio, or the ratio of average left ventricular diastolic thickness to half the ventricular internal diastolic dimension; VST = ventricular septal thickness; ? = uncertain.

vals.[10–13] Although one recent study[13] demonstrated increased ventricular septal and left ventricular wall thickness on echocardiography in approximately 45 percent of a group of chronic alcoholic subjects, another[14] documented no difference from normal controls in variables of cardiac structure and function. However, the patients in the latter study had undergone a prolonged period of abstinence from alcohol (mean 3.1 years, range 3 months to 16 years). Clinical improvement of left ventricular failure was previously reported in patients after complete cessation of alcohol consumption.[3,8,15]

To further investigate possible changes in cardiac structure and function induced by chronic excessive intake of alcohol, we studied chronic alcoholic subjects with and without cardiac symptoms by M mode echocardiography and compared the findings in these two groups with echocardiographic data obtained from normal subjects.[16,17]

Methods

Study Patients

Patients admitted to the Veterans Administration Hospital, Washington, D.C., with a history of chronic alcoholism were evaluated. Patients were classified into two groups: those with and those without overt evidence of heart disease.

Patients without symptoms of cardiac disease: Twenty-two chronic alcoholic patients admitted to the Alcohol Rehabilitation Service at the Veterans Hospital over a 3 month period were evaluated by physical examination, electrocardiography, chest roentgenography and echocardiography. This group of 21 men and 1 woman (age range 31 to 57 years, mean 46) had no symptoms of heart disease and no history compatible with angina pectoris, previous myocardial infarction, valvular heart disease or hypertension. All patients had been heavy drinkers, that is, consuming an average quantity equivalent to at least 12 ounces of whiskey daily for at least 6 years (the majority for greater than 15 years). All patients had abstained from drinking while on the ward for at least 2 weeks before echocardiographic evaluation.

Patients with clinical evidence of cardiomyopathy: Eleven chronic alcoholic patients (aged 28 to 66 years) with cardiac catheterization-proved dilated (congestive) cardiomyopathy[5] also were studied. None had a history compatible with congenital, rheumatic, hypertensive or atherosclerotic heart disease. All patients had a history of chronic alcoholism for more than 10 years, and all had had symptoms of congestive heart failure for 1 to 6 years. At the time of echocardiographic study, three were in New York Heart Association[18] functional class IV, three were in class III, and five in class II (Table I). All had had initial improvement with therapy. The five patients in class II had been more symptomatic at the time of catheterization, but their condition had improved with treatment. Only patients whose clinical status warranted evaluation by cardiac catheterization were included in the symptomatic group.

Normal subjects: Echocardiographic data from patients in both the symptomatic and asymptomatic groups of chronic alcoholics were adjusted for age and body surface area using regression equations derived from 136 normal subjects, which were previously reported from our laboratory.[16,17] No normal subject had a history of heart disease or hypertension and all had normal findings on physical examination, electrocardiography and chest roentgenography. In addition, none had echocardiographic evidence of pericardial effusion or valvular heart disease.

Echocardiography

Echocardiograms were recorded using an Ekoline 20A ultrasound unit, Honeywell 1856 line scan recorder, Hewlett-Packard X-Y display and a custom-built video amplifier.[19] Measurements were made according to the recommendations of the American Society of Echocardiography.[20] Aortic root and left atrial dimensions were recorded by angling the ultrasonic beam from the mitral valve into the aortic root.[21] At this point, minor adjustments of transducer orientation were made until the beam was reflected from the aortic valve leaflets. Measurement of aortic root dimension was made at end-diastole at the onset of the QRS complex; the left atrium was measured at the maximal dimension at end-systole.[20] The posterior wall of the left atrium was identified utilizing a custom-built switched gain circuit.[22]

Ventricular measurements: The internal dimension of the left ventricle at end-diastole was measured at the onset of the QRS complex; the end-systolic dimension was measured at the nadir of septal motion (that is, when the ventricular

TABLE II

Asymptomatic Chronic Alcoholics: Clinical and Echocardiographic Characteristics

Case	Age (yr)	BP	Aus	BSA (cm^2)	LVIDd (mm)	LVIDs (mm)	VST (mm)	LVWT (mm)	ARD (mm)	LAD (mm)	LV % FS	LV Mass (g)	t/r
12	34	110/78	0	1.66	51	35	10	10	32	37	31	237	0.39
13	44	110/64	S_4	1.59	50	32	12	12	29	41	36	294	0.48
14	54	120/70	S_3, S_4	1.59	46	27	12	12	34	34	41	258	0.52
15	46	110/70	S_4	1.75	56	38	11	11	32	32	32	314	0.39
16	57	125/75	S_4	1.84	48	26	12	13	32	44	46	292	0.52
17	39	125/80	0	1.95	48	29	13	13	29	38	40	309	0.54
18	49	124/80	S_4	1.93	56	34	12	12	36	41	39	353	0.43
19	46	110/80	0	1.93	50	31	12	13	30	46	38	312	0.50
20	42	105/75	0	1.82	58	38	12	12	34	44	34	374	0.41
21	50	142/84	S_4	1.97	49	31	11	12	30	39	37	268	0.47
22	57	124/80	S_4	1.79	45	30	11	11	27	39	33	220	0.49
23	44	110/80	0	1.70	44	25	11	11	31	34	43	212	0.50
24	57	130/80	S_4	1.83	50	33	12	12	27	34	34	294	0.48
25	50	115/65	S_4	1.82	55	40	13	13	33	41	27	383	0.47
26	32	120/70	S_3, S_4	1.85	53	33	11	11	30	37	38	287	0.42
27	55	145/72	S_4, P_2	1.61	52	40	11	12	30	38	23	295	0.44
28	42	110/70	S_4	2.08	51	31	14	13	34	42	39	359	0.53
29	46	105/60	S_3	2.14	56	39	11	12	36	40	30	333	0.41
30	46	125/80	S_4	1.86	53	36	11	12	34	35	32	305	0.43
31	49	140/80	Tach	1.86	58	40	11	12	33	35	31	353	0.40
32	45	144/-	S_3	1.79	48	30	14	12	29	36	38	309	0.54
33	31	120/64	0	1.95	50	35	12	11	31	35	30	277	0.46
Mean	46	. . .	. . .	1.84	51	33	12	12	31.5	38	35	302	0.46

Tach = tachycardia; other abbreviations as in Table I.

septum was farthest from the anterior chest wall). Both measurements were made with the ultrasonic beam passing through the left ventricle slightly caudal to the tip of the mitral valve using the T scan technique.[19] The diastolic thickness of the ventricular septum and the left ventricular posterior wall were measured in the same portion of the record used to measure left ventricular internal dimension.[20] Measurements were made at the onset of the QRS complex using the leading edge method and the switch gain circuit to help identify the left ventricular epicardial surface.[20,22]

Percent fractional shortening of the left ventricle was calculated by the formula[23]: (LVIDd − LVIDs)/LVIDd, where LVIDd is end-diastolic dimension and LVIDs is end-systolic dimension.

Left ventricular (LV) mass was estimated as previously described[21,24,25]: LV mass = [1.05] [(LVIDd + IVS + LVPW)^3 − (LVIDd)^3], where IVS denotes the diastolic thickness of the ventricular septum and LVPW represents left ventricular posterior wall thickness.

A diastolic thickness to radius (t/r) ratio for the left ventricle was calculated by the formula:

$$t/r = LVWTa/1/2\ LVIDd,$$

where LVWTa thickness was defined as the average of the diastolic ventricular septal and left ventricular posterior wall thicknesses.

Data analysis: Echocardiographic data for the symptomatic and asymptomatic alcoholic groups are recorded in Tables I and II. These data also were expressed as a percent of the predicted normal value for each variable using age and body surface area, as previously described[16,17] (Fig. 1 to 4). Body surface area was estimated from the height and weight by the Boothby and Sandiford modification[26] of the formula of DuBois and DuBois.[27] The percent predicted data are plotted on graphs for each variable, displaying the 95 percent prediction interval for normal subjects as a percent of the mean (Fig. 1 to 4). The advantage of expressing *each* echocardiographic data point as a percent of the predicted normal value is that it allows the data from each subject to be compared with the normal values and thereby avoids errors in data analysis that might arise from merely adjusting a single group mean echocardiographic value for the mean age and body surface area.

Statistical comparisons of the data in the asymptomatic and symptomatic chronic alcoholic groups with the predicted normal data were performed utilizing F tests and Student's *t* test with appropriate corrections.[28]

Results

Clinical and Hemodynamic Data

Symptomatic chronic alcoholic patients: In every patient, physical examination revealed cardiomegaly with signs of left or biventricular failure in the absence of hypertension. Third and fourth heart sounds and a murmur of mitral regurgitation were the most common abnormal auscultatory findings. Chest roentgenograms revealed generalized cardiomegaly in all with signs of pulmonary venous hypertension in the more severely symptomatic patients. The electrocardiograms all showed left ventricular hypertrophy or interventricular conduction delay, or both. One patient had left bundle branch block, one was in atrial fibrillation at the time of study, and three others had recently had conversion to sinus rhythm from atrial fibrillation. At cardiac catheterization, all patients had left ventricular dilatation with symmetric but hypokinetic wall motion and increased left ventricular end-diastolic pressure; six had evidence of mild and two had evidence of moderate mitral regurgitation. Coronary angiograms were entirely normal in all but four patients. These four patients had only minimal (25 to 50 percent) narrowing of the luminal diameter of one or two vessels, which was not considered hemodynamically significant.

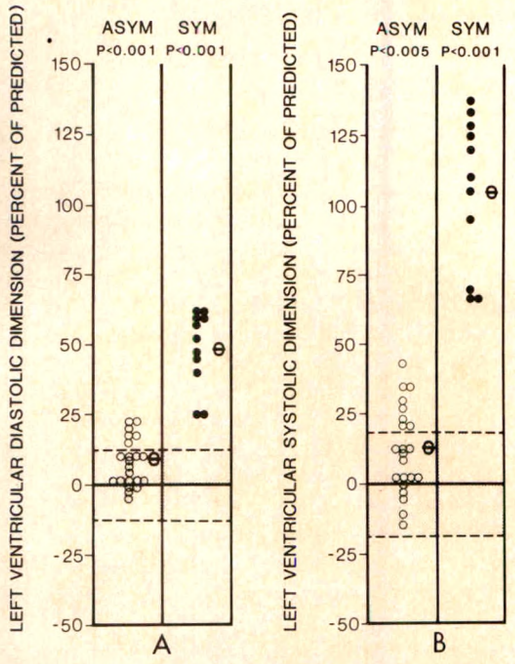

FIGURE 1. Plot of the percent differences between observed and predicted normal values for left ventricular internal dimension in diastole (**A**) and systole (**B**) for 22 asymptomatic (ASYM) (**open circles**) and 11 symptomatic (SYM) (**closed circles**) subjects. The **shaded areas** represent the 95 percent prediction intervals for normal subjects obtained for each echocardiographic variable. Mean percent differences (**open circles with horizontal bar**) are depicted to the right of each group of data points. P = probability.

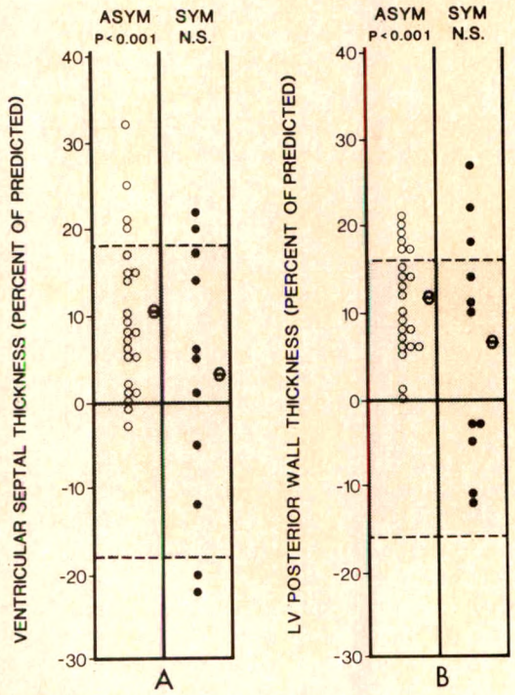

FIGURE 2. Plot of the percent differences between observed and predicted normal values for ventricular septal thickness (**A**) and left ventricular (LV) posterior wall thickness (**B**) for 22 asymptomatic and 11 symptomatic subjects. N.S. = not significant; other abbreviations and format as in Figure 1.

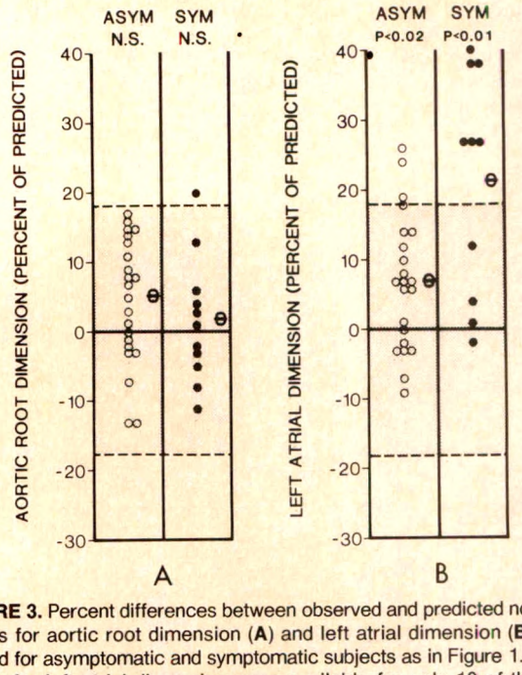

FIGURE 3. Percent differences between observed and predicted normal values for aortic root dimension (**A**) and left atrial dimension (**B**) are plotted for asymptomatic and symptomatic subjects as in Figure 1. Data points for left atrial dimension were available for only 10 of the 11 symptomatic subjects. Abbreviations as before.

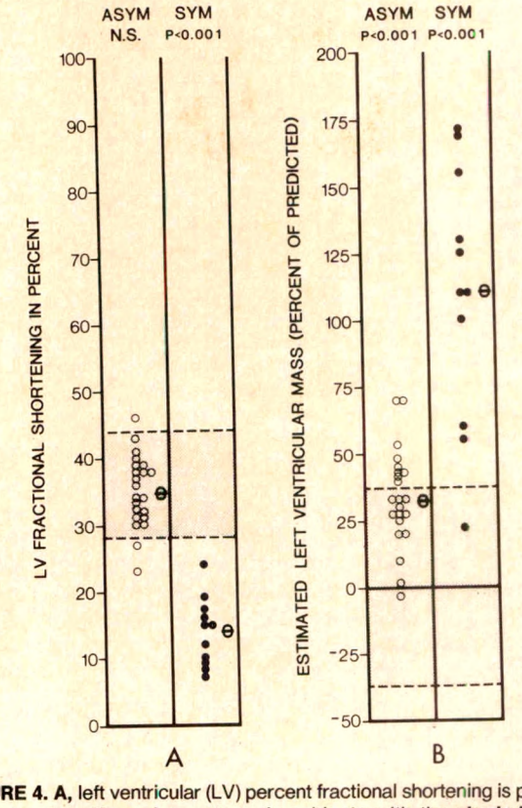

FIGURE 4. A, left ventricular (LV) percent fractional shortening is plotted for asymptomatic and symptomatic subjects with the **shaded area** representing the 95 percent prediction interval for normal subjects (range 28 to 44 percent). **B**, percent differences between observed and predicted normal values for estimated left ventricular mass are plotted. Format and abbreviations as in Figure 1.

TABLE III

Symptomatic and Asymptomatic Chronic Alcoholics: Left Ventricular Variables Expressed as a Percent of Predicted Value

Case	LVIDd	VST	LVWT	t/r
		A. Symptomatic		
1	+25	−22	−3	−28
2	+59	−5	−5	−38
3	+45	+22	+22	−12
4	+62	+20	+11	−25
5	+46	−20	−11	−39
6	+60	+5	+18	−33
7	+52	+17	+27	−18
8	+25	+1	+10	−13
9	+57	+6	−3	−33
10	+39	+14	+14	−14
11	+62	−12	−12	−43
Mean	+48	+2.4	+6.2	−27
SD	13.8	15.6	13.6	11.3
SEM	4.2	4.7	4.1	3.4
		B. Asymptomatic		
12	+10	+1	+1	−5
13	+9	+17	+17	+11
14	+4	+15	+15	+16
15	+20	+6	+5	−10
16	+2	+8	+17	+16
17	−2	+21	+21	+28
18	+16	+9	+9	−2
19	+3	+10	+19	+16
20	+22	+14	+14	−3
21	+1	−1	+8	+7
22	−3	0	0	+8
23	−5	+6	+6	+16
24	+7	+8	+8	+7
25	+17	+20	+20	+7
26	+10	+7	+7	+1
27	+17	+5	+14	−2
28	+2	+27	+18	+24
29	+11	−3	+6	−5
30	+11	+2	+12	0
31	+22	+1	+10	−10
32	+2	+32	+13	+26
33	+1	+15	+6	+12
Mean	+8	+10	+11	+7
SD	8.2	9.3	6.1	11.3
SEM	1.7	2.0	1.3	2.4

All values are expressed as a percent above or below the predicted value calculated for each patient based on size and body surface area. A value of 0 percent means that the actual value corresponds to the predicted value. SD = standard deviation; SEM = standard error of the mean; other abbreviations as in Table I.

Asymptomatic chronic alcoholics: The 22 chronic alcoholics in this group had no symptoms of cardiac decompensation or systemic hypertension. Cardiac examination revealed mild abnormalities in 16 (72 percent) of these patients (Table II): A fourth heart sound was present in 13 patients, a third heart sound in 4 (18 percent), an increased pulmonary component of the second heart sound (P_2) in 1 (4 percent) and tachycardia in 1. Chest roentgenograms in this group revealed no cardiomegaly or evidence of pulmonary venous hypertension. Electrocardiograms were normal or nonspecific, demonstrating sinus tachycardia in one patient (4 percent), left axis deviation in two patients (8 percent) and nonspecific ST-T wave abnormalities in four patients (18 percent).

Echocardiographic Data

Left ventricular internal dimension (Fig. 1, Tables I to III): Left ventricular internal dimension at end-diastole and at end-systole was increased in all 11 symptomatic patients. Mean left ventricular end-diastolic dimension was increased 48 percent above the mean normal value ($p < 0.001$), whereas mean left ventricular end-systolic dimension was increased 105 percent above the normal mean ($p < 0.001$). Among the 22 asymptomatic chronic alcoholics, left ventricular diastolic dimension was above the 95 percent normal prediction interval in 6 (27 percent), and systolic dimension was outside the 95 percent normal prediction interval in 8 patients (36 percent). Mean left ventricular diastolic dimension was 8 percent above the normal mean, whereas mean systolic dimension was 12 percent above the normal mean; both of these differences were statistically significant ($p < 0.001$ and < 0.005, respectively).

Ventricular septal and left ventricular posterior wall thickness (Fig. 2, Tables I to III): All patients in both the symptomatic and asymptomatic groups had a ventricular septal to left ventricular posterior wall thickness ratio of less than 1.3 to 1. Ventricular septal thickness was above the 95 percent normal prediction interval in 2 of the 11 symptomatic patients. In two other symptomatic patients, values were below the mean by a similar percent. Mean ventricular septal thickness was 2.4 percent above the normal mean, but this difference was not statistically significant. In contrast, among the 22 asymptomatic patients, 4 (18 percent) had values above and none had values below the normal 95 percent prediction interval. On average, mean ventricular septal thickness was 10 percent above the normal, a statistically significant difference ($p < 0.001$).

Left ventricular posterior wall thickness in diastole was above the normal prediction interval in 3 (27 percent) of the 11 symptomatic patients and below normal in none. Only one of these three patients (Case 3) had a ventricular septal thickness also above the normal prediction interval. Mean left ventricular wall thickness in the symptomatic group was 6 percent above normal (not a significant difference). In the asymptomatic group, 6 (27 percent) of 22 patients had left ventricular posterior wall thickness above the normal range and, again, none had values below this range. The 11 percent mean increase of left ventricular wall thickness above the normal mean was statistically significant ($p < 0.001$).

Aortic root and left atrial dimensions (Fig. 3, Tables I and II): Aortic root dimension was outside the prediction interval in only one symptomatic patient. Mean aortic root dimension in this group was not statistically different from normal (1.6 percent above normal mean). All 22 asymptomatic patients had a value for aortic root dimension falling within the 95 percent

prediction interval. In this asymptomatic group, the mean aortic root dimension (5 percent above normal mean) was not significantly different from normal.

Left atrial dimension was above the normal interval in 6 (60 percent) of 10 symptomatic patients (mean value 21 percent above the normal mean; $p < 0.01$). The presence of a significantly increased left atrial dimension was not positively correlated with the presence or absence of increased ventricular septal thickness or left ventricular wall thickness in the symptomatic group. (All symptomatic patients had increased left ventricular systolic and diastolic internal dimensions.) Only three (14 percent) of the asymptomatic patients had an increased left atrial dimension. Nonetheless, the mean increase in this group (7 percent) was significantly different from the normal mean ($p < 0.02$).

Left ventricular percent fractional shortening (Fig. 4A, 5A, Tables I and II): All 11 symptomatic patients had left ventricular systolic dysfunction as manifested by a left ventricular percent fractional shortening significantly ($p < 0.001$) below the normal range of 28 to 44 percent. Mean left ventricular percent fractional shortening in the symptomatic group was only 14 percent. Among the asymptomatic patients, one had a percent fractional shortening above the normal interval, and two had a value below this interval. The mean left ventricular percent fractional shortening in this group was 35 percent, a value not statistically different from the normal mean of 36 percent. Thus, on average, the asymptomatic group did not exhibit abnormal left ventricular systolic function.

When the data for left ventricular percent fractional shortening were plotted against the left ventricular internal dimension in diastole, an interesting trend became apparent. When the asymptomatic patients were classified into those with a left ventricular diastolic dimension less than 10 percent above the normal predicted value and those with a diastolic dimension 10 to 24 percent above the predicted value, the mean left ventricular percent fractional shortening in the two groups was 38 and 32 percent, respectively. This difference was significant ($p < 0.01$) (Fig. 5A). The symptomatic patients, all of whom had a left ventricular internal dimension greater than 25 percent above the normal mean predicted value, had a mean left ventricular percent fractional shortening of 14 percent. Although the symptomatic patients with a dilated left ventricle obviously had a lower percent fractional shortening, there was also a trend toward a smaller (albeit within normal range) fractional shortening percent in the asymptomatic patients with a larger (10 to 24 percent above predicted value) left ventricular diastolic dimension.

Left ventricular mass (Fig. 4B, Tables I and II): All but 1 of the 11 symptomatic patients had an estimated left ventricular mass above the normal interval. The mean left ventricular mass in this group (493 g) was 110 percent above the normal mean, a significant difference ($p < 0.001$). In addition, 9 of the 22 asymptomatic patients had an estimated left ventricular mass

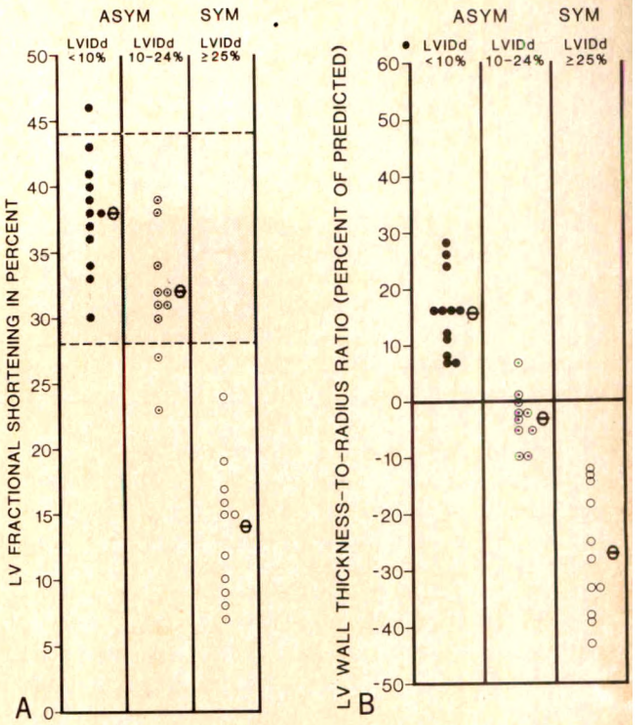

FIGURE 5. A, left ventricular percent fractional shortening is plotted for two asymptomatic subgroups, one with left ventricular diastolic dimension (LVIDd) less than 10 percent above the normal predicted, the second with LVIDd 10 to 24 percent above normal; and for symptomatic patients, all of whom had a diastolic dimension 25 percent or greater above normal. The **shaded area** represents the 95 percent normal prediction interval for percent fractional shortening. **B,** percent differences between observed and predicted normal values for left ventricular (LV) wall thickness to radius ratio are plotted for the two asymptomatic groups and the symptomatic patients. Abbreviations and format as in Figure 1.

above the normal range. The mean left ventricular mass in the asymptomatic group (302 g) was 33 percent above the estimated normal mean; this difference was also significant ($p < 0.001$).

Left ventricular thickness to radius ratio (Fig. 5B, Tables I to III): All 11 symptomatic patients demonstrated a subnormal diastolic thickness to radius ratio of the left ventricle, the mean being 27 percent below the normal predicted mean value. The asymptomatic group, on the other hand, had a mean thickness to radius ratio 7 percent above the normal value. Moreover, when the asymptomatic patients were classified into two subgroups based on left ventricular diastolic dimensions, that is, one group with a diastolic dimension less than 10 percent and another group with a diastolic dimension of 10 to 24 percent, the mean values for thickness to radius ratio of the left ventricle expressed as a percent of predicted were +16 and −3 percent, respectively. Of further interest, patients in the symptomatic group, all of whom had a left ventricular diastolic dimension greater than 25 percent above the predicted normal, had a thickness to radius ratio below the range

found in the asymptomatic patients. The differences among the three subgroups in the mean left ventricular wall thickness to radius ratios expressed as a percent of the predicted value were statistically significant ($p < 0.01$).

Clinical and Echocardiographic Comparison

Symptomatic chronic alcoholics: As expected, the echocardiographic findings of increased left ventricular and left atrial dimensions, increased left ventricular mass and decreased left ventricular percent fractional shortening correlated well with the physical findings of cardiomegaly and left or biventricular failure (third and fourth heart sounds) with or without mitral regurgitation.

Asymptomatic chronic alcoholics: Although 16 patients had abnormal physical findings, a fourth heart sound was the only abnormal finding in 10 patients. Eleven of these 16 patients had at least one abnormal echocardiographic finding among the following: left ventricular systolic or diastolic dimension, ventricular septal thickness or left ventricular wall thickness, left atrial dimension and estimated left ventricular mass. Both the patient with tachycardia and the patient with an increased intensity of the pulmonary component of the second heart sound had abnormal echocardiographic findings. Of the four patients with a third heart sound, two (50 percent) had significant echocardiographic abnormalities. However, four (67 percent) of the six patients without any abnormal physical findings also had one or more abnormal echocardiographic findings. Consequently, the presence or absence of significant echocardiographic abnormalities did not correlate well with the presence or absence of a third or fourth heart sound. Similarly, auscultatory findings could not predict whether an asymptomatic patient would fall into the subgroup with left ventricular diastolic dimension less than 10 percent or 10 to 24 percent above the predicted value.

Discussion

Alcoholic cardiomyopathy: Previous echocardiographic studies[6,7] in chronic alcoholics who have symptomatic heart disease have demonstrated increased left ventricular diastolic and systolic dimensions, markedly decreased ventricular septal and posterior left ventricular wall excursion and decreased left ventricular percent fractional shortening. In some patients, mild concentric left ventricular thickening on angiography has been reported.[5] In the present study, all 11 of the chronic alcoholic patients with physical findings of biventricular failure and catheterization-proved dilated (congestive) cardiomyopathy had echocardiographic evidence of increased left ventricular and left atrial dimensions, increased left ventricular mass and decreased left ventricular percent fractional shortening. All but one of these patients had a significant increase in estimated left ventricular mass. Although three of these patients had increased left ventricular posterior wall thickness and two had increased ventricular septal thickness, two others had *decreased* ventricular septal thickness. None of these abnormalities in septal or ventricular wall thickness were statistically significant.

Role of mitral regurgitation: Eight of our 11 symptomatic patients had mild to moderate mitral regurgitation. Although it is impossible to determine precisely the relative contributions of myocardial dysfunction versus mitral regurgitation in producing the increases in chamber dimensions and left ventricular mass and the decrease in left ventricular percent fractional shortening, several points are clear. First, the presence of mitral regurgitation was not necessary for the left ventricular dilatation and decompensation seen in these chronic alcoholic patients: Three of our 11 patients did not have mitral regurgitation. Second, the mitral regurgitation in our symptomatic patients had no obvious cause other than alcoholic heart disease; presumably, mitral regurgitation was caused by the abnormal mitral leaflet coaptation resulting from left ventricular dilatation. Finally, the left ventricle in our symptomatic alcoholics with mitral regurgitation differed markedly from that in 10 patients whom we have studied with mitral regurgitation on the basis of either rheumatic heart disease, ruptured chordae tendineae or mitral valve prolapse. Although the left ventricular diastolic dimensions were comparable in the two groups of patients, left ventricular percent fractional shortening was either normal or increased in our 10 patients with primary mitral regurgitation but was markedly decreased in our symptomatic chronic alcoholic patients (unpublished observations). Similar observations in patients with mitral regurgitation have previously been reported.[29]

Ventricular dysfunction in asymptomatic alcoholic patients: Although the changes in cardiac structure and function that occur after the development of the clinical findings of dilated cardiomyopathy have been well established, the cardiac findings in chronic alcoholics during the asymptomatic period have been less completely defined. Regan et al.[8] demonstrated that the left ventricle in chronic alcoholics without cardiac symptoms responds abnormally (with decreased left ventricular contractility and an abnormal increase in end-diastolic pressure) to increments in afterload compared with findings in nonalcoholic control subjects. Spodick and Zambrano and co-workers[10,11] and Wu et al.[12] studied chronic alcoholics who had no cardiac symptoms, and both groups found abnormal systolic time intervals indicative of left ventricular dysfunction. The alcoholics studied by Spodick et al were examined 2 to 3 days after their last ingestion of alcohol whereas those investigated by Wu et al. had abstained for a mean of 12 days (range 4 to 60). Reeves et al.[14] studied chronic alcoholics without overt heart disease by M mode echocardiography and documented no difference from normal control subjects in various structural and functional variables. However, the patients in their study had undergone a prolonged period of abstinence from alcohol (mean 3.1 years; range 3 months to 17 years).

The 22 asymptomatic patients in our study, who were studied after only 2 weeks to 3 months of abstinence from alcohol, are more similar in clinical status to the patients of Spodick,[10] Zambrano,[11] Wu,[12] and Askanas[13] and their co-workers than to those studied by Reeves et al.[14] Fifteen (68 percent) of our 22 patients had at least one significant abnormality on echocardiography after the data were adjusted for age and body surface area. The most frequent abnormality (not considering thickness to radius ratio) was an increase in estimated left ventricular mass, observed in nine patients. Seven patients had increased left ventricular internal dimension (systolic or diastolic, or both), six had increased wall thickness (septal or left ventricular posterior, or both), one had both increased left ventricular dimensions and wall thickness and three had increased left atrial dimension.

The asymptomatic as well as the symptomatic patients exhibited significant mean increases in left ventricular internal dimensions, left atrial dimension and estimated left ventricular mass compared with normal subjects, but these increases, not unexpectedly, were much greater in the symptomatic group. The asymptomatic patients differed from the symptomatic patients in demonstrating a significant, albeit small (10 to 11 percent), increase in mean (septal and left ventricular posterior) wall thickness while maintaining a normal mean left ventricular percent fractional shortening. Although these echocardiographic findings are similar to those of Askanas et al.,[13] the mean increases in ventricular septal and left ventricular wall thickness (22 and 19 percent, respectively) they reported in their chronic alcoholic patients were somewhat greater than in our group.

Additional insight into the asymptomatic chronic alcoholics was obtained by classifying these patients into two subgroups on the basis of left ventricular diastolic dimension. One group, with a left ventricular diastolic dimension less than 10 percent above the normal predicted value, had an average wall thickness increased out of proportion to the increased left ventricular diastolic dimension (mean thickness to radius ratio +16 percent above normal predicted), and a mean left ventricular percent fractional shortening of 38 percent that, although normal, was slightly above the normal mean of 36 percent. The second group, with left ventricular diastolic dimensions ranging from 10 to 24 percent above the normal, had a mean left ventricular wall thickness to radius ratio (mean −3 percent) slightly below normal and a mean left ventricular percent fractional shortening of 32 percent that, although normal, was below the normal mean. The symptomatic patients, all of whom had a left ventricular diastolic dimension greater than 25 percent above the normal predicted value, had a significantly decreased left ventricular thickness to radius ratio (mean −27 percent below predicted) and left ventricular percent fractional shortening (mean 14 percent). Clinically, the presence and type of echocardiographic abnormalities in both subgroups of asymptomatic patients were not reliably predicted by the presence on auscultation of a third or fourth heart sound.

Models of preclinical stages of alcoholic heart disease: Our data are generally in agreement with the work of Ford[30] and Grossman et al.,[31] who suggested that, in the compensated left ventricle, the myocardial fibers undergo hypertrophy, that is, left ventricular wall thickness increases, with increases in left ventricular dimension (volume) in order to normalize wall stress. In this regard, our echocardiographic data in the asymptomatic subjects are compatible with two models that might explain the response of the left ventricle to a toxic substance such as alcohol. The first model postulates that every asymptomatic subject goes through an initial stage in which there is mild left ventricular dilatation with an increase in left ventricular wall thickness that is proportionately greater than the increase in internal dimension, resulting in an increased thickness to radius ratio. At this point, left ventricular function is normal. Subsequently, with continued consumption of alcohol, left ventricular dilatation progresses, but wall thickening does not keep pace, yielding a thickness to radius ratio which is slightly decreased. Left ventricular wall stress at this stage is presumably normal or nearly normal, and systolic function is beginning to be impaired. Finally, with ventricular decompensation, left ventricular dilatation is markedly increased but the left ventricular thickness to radius ratio is decreased, which results in a significant increase in left ventricular wall stress. A second model postulates that there are two distinct subgroups of asymptomatic subjects whose hearts respond differently to the damage produced by alcohol. One group exhibits mild left ventricular dilatation with a proportionately greater increase in wall thickness associated with an increased thickness to radius ratio, normal or reduced wall stress and normal or increased percent fractional shortening. Patients who respond this way may have a stable clinical course and be relatively resistant to the toxic effects of alcohol on the heart. A second group, destined to have left ventricular decompensation (dilatation and decreased percent fractional shortening) with continued alcohol intake, responds to chronic consumption of alcohol with a moderately increased left ventricular internal dimension and a proportionately smaller increase in wall thickness. The resultant left ventricular thickness to radius ratio is normal or slightly decreased, and the percent fractional shortening is in the lower range of normal. Patients in this second group may be destined, with continued consumption of alcohol, to progress to the end stage cardiomyopathy characteristic of our symptomatic patients.

Implications: These models of the clinical spectrum of alcoholic heart disease are, of course, only speculative. Long-term prospective studies of a large number of chronic alcoholic subjects are required before it can be determined whether one of these models accurately explains the clinical progression of patients from an early stage of mild left ventricular dilatation and wall thickening with normal systolic function to the end

stage of overt, clinically apparent decompensation. If prospective studies confirm these speculations, echocardiography should prove very useful clinically as a method for identifying specific patients at high risk of developing cardiomyopathy. Special efforts could then be made to convince these high risk patients to stop their consumption of alcohol.

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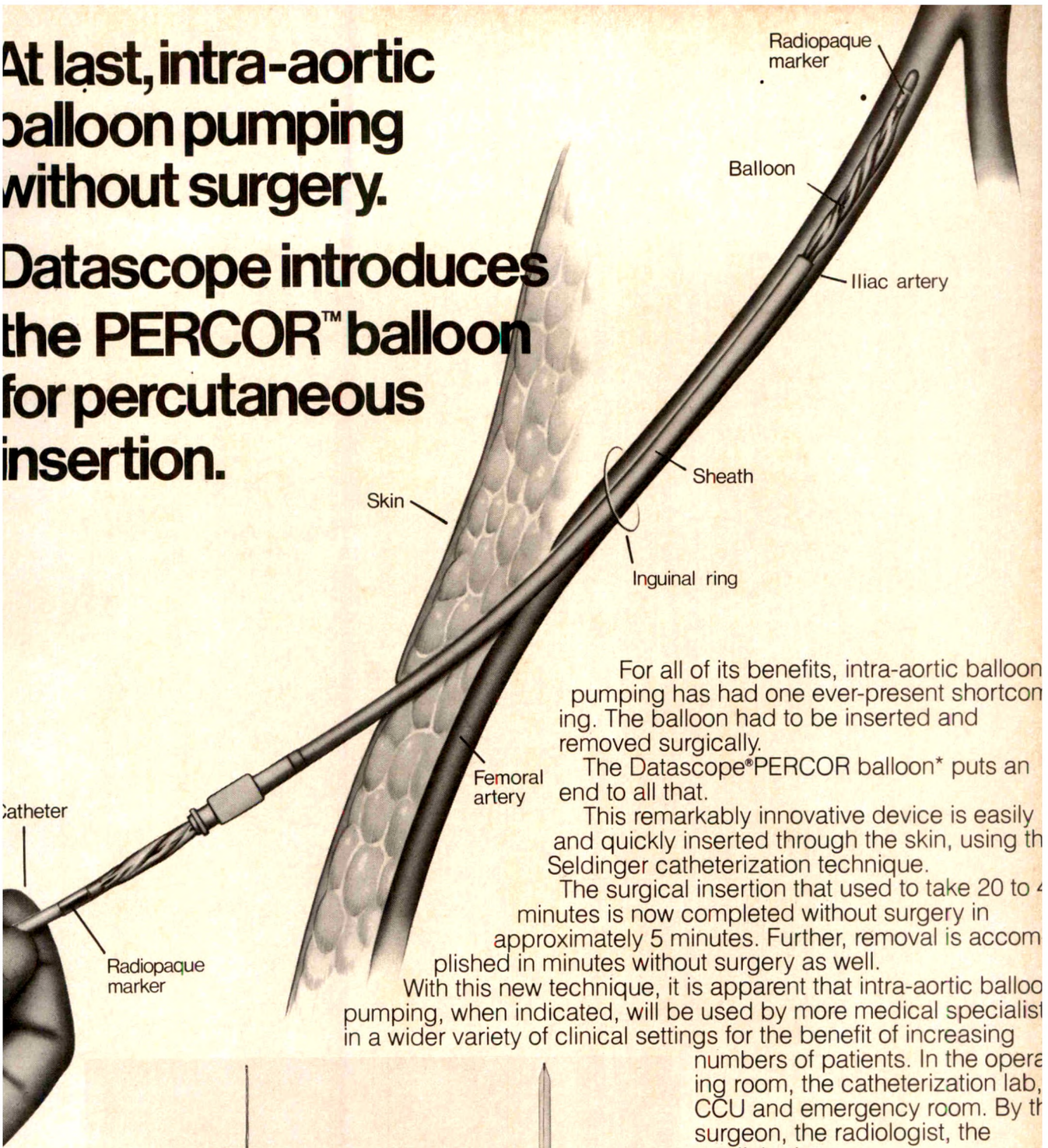

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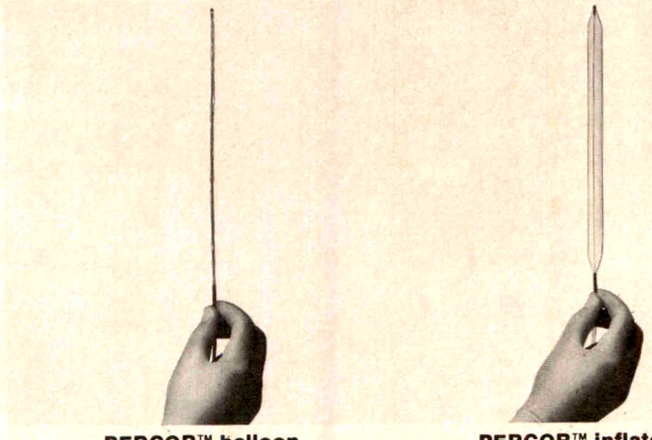

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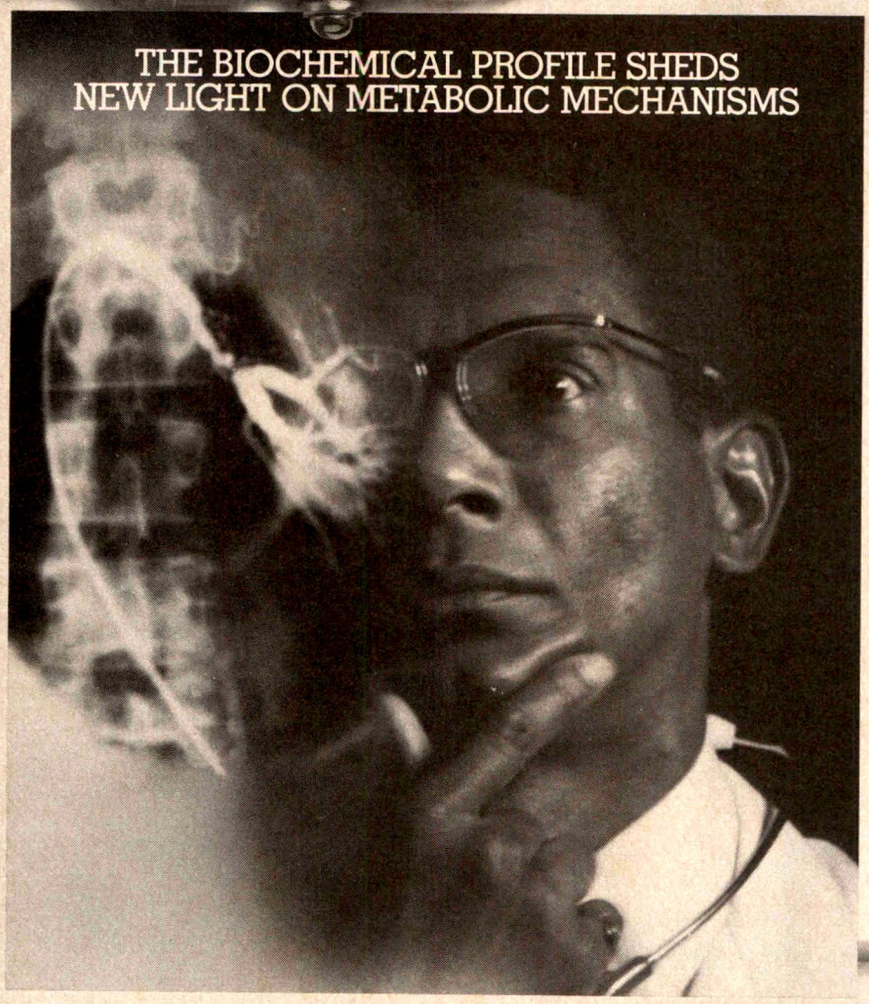
"PROFILING" TODAY'S HYPERTENSIVE PATIENT



THE BIOCHEMICAL PROFILE SHEDS NEW LIGHT ON METABOLIC MECHANISMS

While hypertension still remains an enigma, its metabolic pathways have become clearer in the past twenty years. One of the most important pathways involves the renin-angiotensin-aldosterone system. The kidney is known to secrete renin under three circumstances: 1) when the organ itself becomes ischemic; 2) when the body's sodium content is depressed; 3) when blood volume is reduced. Renin then catalyzes the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II. Besides being the most potent vasopressor known,[1] angiotensin II also stimulates the adrenal gland to produce aldosterone. By enhancing renal reabsorption of sodium, aldosterone expands the body's sodium content and plasma volume. This reduces renin production and closes the loops of the negative feedback system. A breakdown in this system may result in higher levels of renin and angiotensin II—and sustained high blood pressure.

Disturbances in other mechanisms can also trigger metabolic chains of events that lead to hypertension. This increasing knowledge has generated interest in drugs designed to halt the hypertensive process at several points. One of the newest drugs is thought to inhibit the enzyme that converts angiotensin I into angiotensin II.[1] Equally important has been the development of more accurate diagnostic tests for "biochemical" profiling.

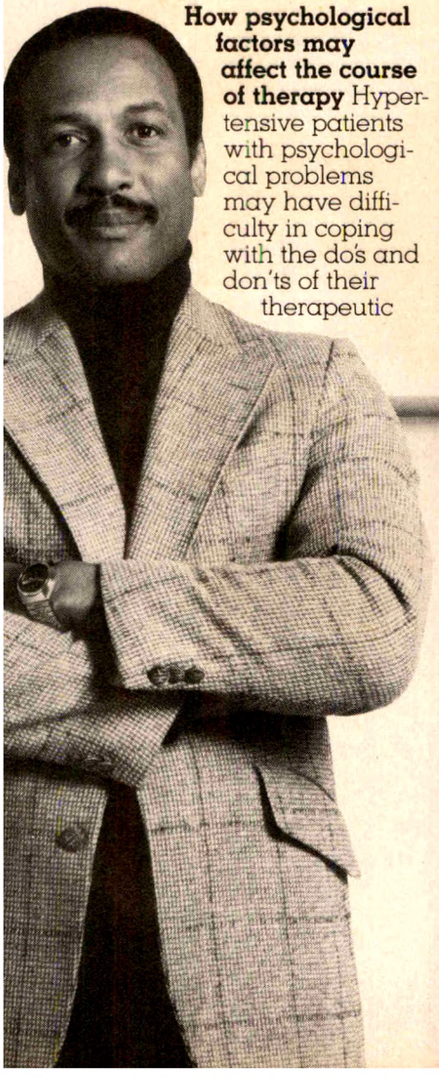
How useful is measuring renin activity? Some clinicians now advocate "renin profiling" of all hypertensives. This rather complicated test provides the renin-sodium index by indirectly measuring the renin level and comparing it to sodium intake. The index helps distinguish renin-dependent hypertensives (about 70% of patients) from those who are sodium-dependent. It is only the latter who are most likely to benefit from diuretics and the "stepped-care" approach.

While renin profiling can be very useful for selected patients, most physicians consider it unnecessary or impractical for routine evaluation. The initial choice of therapy rarely hinges on renin activity.[2] Also, the renin-sodium index is hard to obtain in non-hospitalized patients and may not offer any real advantages over a therapeutic trial that includes a diuretic (for low-renin patients) or a beta blocker (for high-renin patients).[2,3]

The lab workup that works for most patients Some authorities believe that a minimal workup is sufficient for roughly 90% of hypertensive patients.[3] This generally includes a hematologic profile, urinalysis, blood chemistry (covering a number of biochemical variables), along with the standard ECG and chest roentgenogram.[2,3] More exhaustive tests—including renal profiling, intravenous urograms and catecholamine level determinations—would only be ordered if secondary causes are suspected.

THE "PSYCHOLOGICAL PROFILE" ADDS VALUABLE INSIGHTS

At times, it reveals excessive anxiety A good deal of research has focused on the contributory role of psychological and social factors in the development of hypertension. Such factors have been found to increase plasma renin activity.[4] Consequently it is often recommended that some form of psychosocial profile be added to the patient's family and medical history.[2,5] Even though the hypertensive patient may seem calm, a few carefully worded questions often uncover intense psychic tension. The patient's anxiety may center on his psychological problems alone or may extend to the economic and social repercussions of his illness.



How psychological factors may affect the course of therapy Hypertensive patients with psychological problems may have difficulty in coping with the do's and don'ts of their therapeutic program... and with demoralizing new self-images as "chronically sick, potentially dependent" persons. The psychological profile helps the physician assess the patient's understanding of his illness, his emotional reactions to it, and the likelihood of his compliance with recommended therapy. This information can help set the stage for the mutually rewarding doctor-patient rapport essential to successful long-term management of any chronic illness.

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References: 1. Fighting high blood pressure with consciousness-raising, drug innovation and new zeal for dieting. *Med World News 20*(13):34-44, June 25, 1979. **2.** Caldwell JR: *Postgrad Med 65*(5): 66-77, May 1979. **3.** Rakel RE, *et al: Primary Cardiol 5*: 102-109, Sept 1979. **4.** Clamage DM, Vander AJ, Nouw DR: *Psychosom Med 39*: 393-401, Nov-Dec 1977. **5.** Perloff D: *Geriatrics 31*: 77-83, Jan 1976.

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The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies. The physician should periodically reassess the usefulness of the drug for the individual patient.
Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months. After extended therapy, gradually taper dosage. Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence.

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.
Dosage: Individualize for maximum beneficial effect. *Adults:* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d. to q.i.d.; alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d. or q.i.d. as needed; adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d. or q.i.d.; adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d. *Geriatric or debilitated patients:* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated. (See Precautions.) *Children:* 1 to 2½ mg t.i.d. or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
Supplied: Valium® (diazepam/Roche) Tablets, 2 mg, 5 mg and 10 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available in trays of 10.

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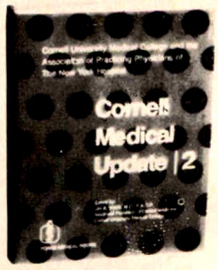

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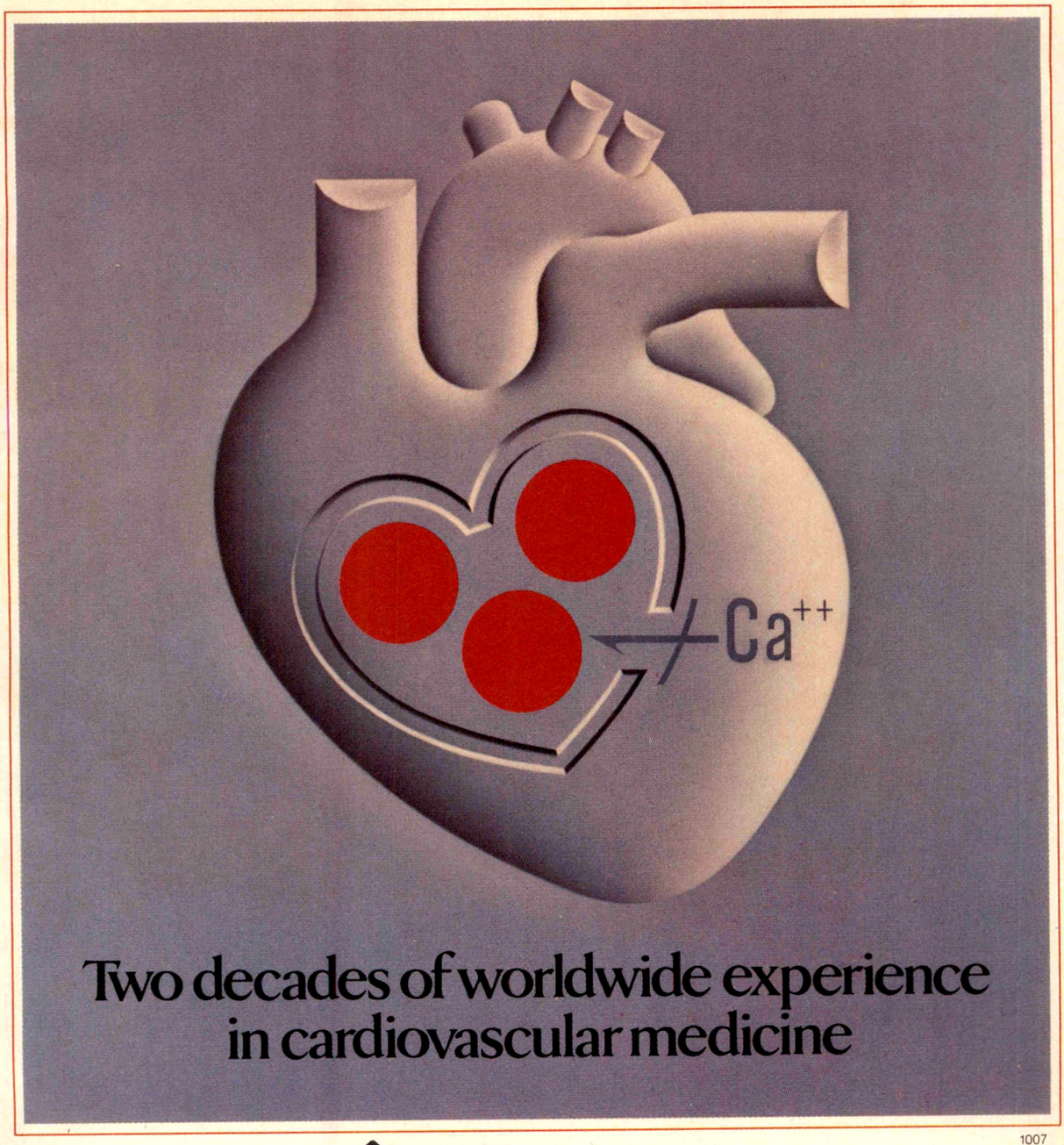

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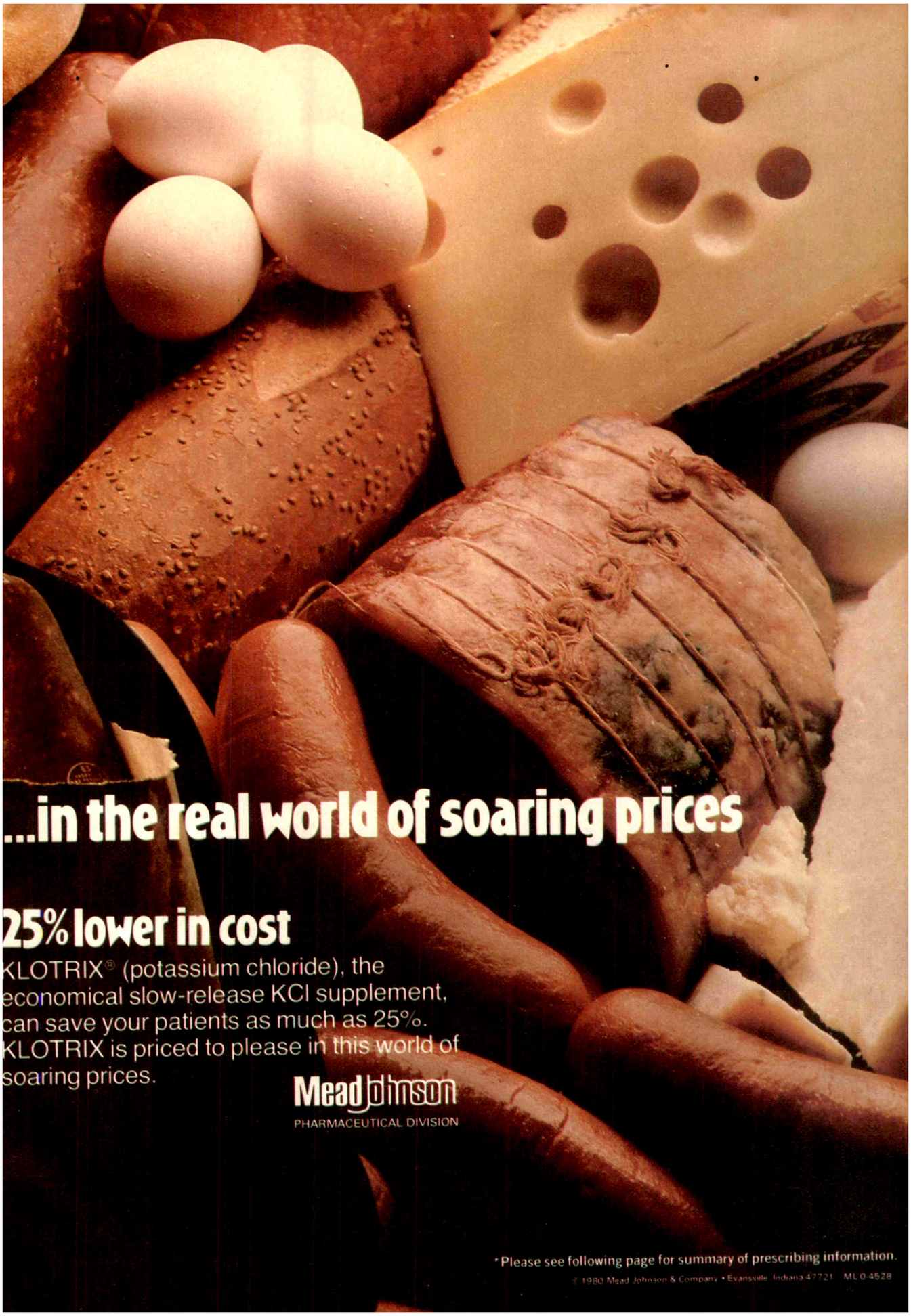
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NEW KLOTRIX®

(POTASSIUM CHLORIDE)
SLOW-RELEASE TABLETS 10 mEq

DESCRIPTION KLOTRIX is a film-coated (not enteric-coated) tablet containing 750 mg potassium chloride (equivalent to 10 mEq) in a wax matrix. This formulation is intended to provide a controlled release of potassium from the matrix to minimize the likelihood of producing high localized concentrations of potassium within the gastrointestinal tract.

INDICATIONS— BECAUSE OF REPORTS OF INTESTINAL AND GASTRIC ULCERATION AND BLEEDING WITH SLOW-RELEASE POTASSIUM CHLORIDE PREPARATIONS, THESE DRUGS SHOULD BE RESERVED FOR THOSE PATIENTS WHO CANNOT TOLERATE OR REFUSE TO TAKE LIQUID OR EFFERVESCENT POTASSIUM PREPARATIONS OR FOR PATIENTS IN WHOM THERE IS A PROBLEM OF COMPLIANCE WITH THESE PREPARATIONS.

1. For therapeutic use in patients with hypokalemia with or without metabolic alkalosis; in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.
2. For prevention of potassium depletion when the dietary intake of potassium is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites; states of aldosterone excess with normal renal function; potassium-losing nephropathy, and certain diarrheal states.
3. The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and, if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

CONTRAINDICATIONS In patients with hyperkalemia, since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (*eg,* spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium.

All solid dosage forms of potassium supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the G.I. tract. In these instances, potassium supplementation should be with a liquid preparation.

WARNINGS Hyperkalemia: In patients with impaired mechanisms for excreting potassium, administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium intravenously but may also occur when given orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. Use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with potassium-sparing diuretics: Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (*eg,* spironolactone or triamterene), since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal lesions: Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. KLOTRIX is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small-bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient-years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient-years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient-years. KLOTRIX should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic acidosis: Hypokalemia in patients with metabolic *acidosis* should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, or potassium acetate.

PRECAUTIONS Potassium depletion is ordinarily diagnosed by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis *per se* can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis *per se* can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. Treatment of potassium depletion particularly in presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, electrocardiogram and clinical status of patient.

ADVERSE REACTIONS Most common to oral potassium salts: nausea, vomiting, abdominal discomfort, and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose. One of the most severe adverse effects is hyperkalemia (see Contraindications and Warnings). There also have been reports of upper and lower gastrointestinal conditions including obstruction, bleeding, ulceration and perforation (see Contraindications and Warnings); other factors known to be associated with such conditions were present in many of these patients. Skin rash has been reported rarely.

DOSAGE Usual dietary intake potassium by the average adult is 40 to 80 mEq per day. Potassium depletion sufficient to cause hypokalemia usually requires loss of 200 or more mEq of potassium from the total body store.

Dosage must be adjusted to the individual needs of each patient but is typically in the range of 20 mEq per day for prevention of hypokalemia to 40-100 mEq per day or more for treatment of potassium depletion.

Note: KLOTRIX slow-release tablets must be swallowed whole and never crushed or chewed.

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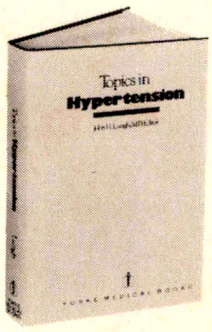

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Antiarrhythmia Bulletin No. 2

Quinidine Withdrawal or Replacement May Decrease Physiologic Effect of Digoxin

Some Further Reports on Problems Arising From the Quinidine-Digoxin Interaction

"An increase in serum digoxin concentration after quinidine is added is now anticipated by many physicians. The opposite is predictable from this observation: a fall in the serum concentration and physiologic effect of digoxin when quinidine is withdrawn from a patient previously stable on both drugs. Although an example of this fall has been reported, little emphasis has been given to this aspect of the quinidine-digoxin interaction, which may have important consequences....

"It appears that this [a 62-year-old female] patient's symptoms and increase in ventricular rate were due to a decrease in serum digoxin concentration and physiologic effect caused by withdrawal of quinidine. This phenomenon should be anticipated when quinidine is discontinued or replaced by other antiarrhythmic therapy in patients previously stable on digoxin and quinidine, especially those in atrial fibrillation, and may require an appropriate readjustment of digoxin dosage based on clinical observations and measured serum digoxin concentrations."

—From Moench, T.R.: The Quinidine-Digoxin Interaction, N. Engl. J. Med. *302*:864, 1980.

"Dr. Moench reports a case that supports the view that quinidine withdrawal can decrease the effect of digoxin. The end point in his study was the time-honored ventricular response to atrial fibrillation, i.e., atrioventricular nodal conduction. His case report provides another bit of evidence that the change in serum digoxin concentration during the interaction often reflects the effect of digoxin on the heart. This hypothesis is difficult to test, and the observations of Dr. Moench are helpful in view of the increasingly complex picture of the interaction."

—From Bigger, J.T., Jr.: The Quinidine-Digoxin Interaction, N. Engl. J. Med. *302*:864–865, 1980.

Do Other Antiarrhythmics Interact With Digoxin?

"We compared the effects of quinidine and three alternate antiarrhythmic drugs on serum digoxin concentration in 63 patients before and during administration of quinidine, procainamide, disopyramide, or mexiletine. Quinidine increased digoxin concentration by at least 0.5 nmol/L in 21 of 22 patients: Mean serum digoxin rose from 1.2 nmol/L to 2.4 nmol/L ($P<0.001$). Procainamide, disopyramide, or mexiletine increased serum digoxin by 0.5 nmol/L in one of 41 patients. Anorexia, nausea, and vomiting developed soon after starting quinidine therapy in 10 of the 22 patients who received quinidine but in only five of the 41 patients who received procainamide, disopyramide, or mexiletine ($P<0.01$). Quinidine prolonged the PR interval from 160 ± 14 ms to 183 ± 26 ms, but procainamide, disopyramide, and mexiletine did not change the PR interval ($P < 0.005$). In digitalized patients, quinidine increases serum digoxin concentration, increases digoxin's effect on atrioventricular conduction, and produces more adverse gastrointestinal effects than procainamide, disopyramide, or mexiletine....

"Figure 1 shows the change in serum digoxin concentrations during administration of the four antiarrhythmic drugs. Each dot represents, for one patient, the difference between the mean serum digoxin concentration before and during therapy with quinidine, procainamide, disopyramide, or mexiletine....

"Because interaction between digoxin and quinidine is common and because quinidine's potential for producing toxicity is still unknown, we recommend that caution be exercised when quinidine is given to digitalized patients....

"Our study shows that several other orally active antiarrhythmic drugs fail to cause an increase in serum digoxin concentration."

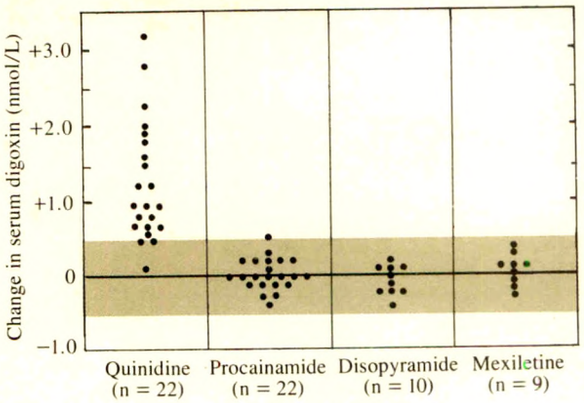


Figure 1.

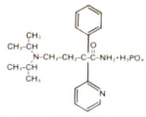
—From Leahey, E.B., Jr., and others: The Effect of Quinidine and Other Oral Antiarrhythmic Drugs on Serum Digoxin: A Prospective Study, Ann. Intern. Med. *92*:605–608, 1980.

From what has appeared in the literature concerning the elevation of digoxin levels with concomitant quinidine use and reported lack of elevation of digoxin levels with concomitant Norpace® (disopyramide phosphate) use, it would appear that Norpace could be a logical alternative to quinidine in some patients using digoxin concomitantly.

NORPACE® CAPSULES (disopyramide phosphate)

DESCRIPTION

Norpace (disopyramide phosphate) is an antiarrhythmic drug available for oral administration in capsules containing 100 mg or 150 mg of disopyramide base, present as the phosphate. The base content of the phosphate salt is 77.6%. The structural formula of Norpace is seen at the right. Norpace is freely soluble in water, and the free base (pKa 8.36) has an aqueous solubility of 1 mg/ml. The chloroform water partition coefficient of the base is 3.1 at pH 7.2. Norpace is a racemic mixture of *d*- and *l*-isomers. This drug is not chemically related to other antiarrhythmic drugs.



α-[2-(diisopropylamino) ethyl]-α-phenyl-2-pyridineacetamide phosphate

CLINICAL PHARMACOLOGY

Mechanisms of action: Norpace (disopyramide phosphate) is a Type 1 antiarrhythmic drug (i.e., similar to procainamide and quinidine). *In animal studies* Norpace decreases the rate of diastolic depolarization (phase 4) in cells with augmented automaticity; decreases the upstroke velocity (phase 0) and increases the action potential duration of normal cardiac cells; decreases the disparity in refractoriness between infarcted and adjacent normally perfused myocardium and has no effect on alpha- or beta-adrenergic receptors.

Electrophysiology: In man, Norpace at therapeutic plasma levels shortens the sinus node recovery time; lengthens the effective refractory period of the atrium and has a minimal effect on the effective refractory period of the AV node. Little effect has been shown on AV-nodal and His-Purkinje conduction times or QRS duration. However, prolongation of conduction in accessory pathways occurs.

Hemodynamics: At recommended oral doses, Norpace rarely produces significant alterations of blood pressure in patients without congestive heart failure (see *Warnings*). Intravenous injection (2 mg/kg over 3 minutes) produces a moderate, transient increase in heart rate and in total peripheral resistance. In patients with organic heart disease intravenous Norpace causes cardiac depression, with approximately a 10% reduction of cardiac output.

Anticholinergic activity: The *in vitro* anticholinergic activity of Norpace is approximately 0.06% that of atropine; however, the usual dose of Norpace is 150 mg every 6 hours compared to 0.4-0.6 mg for atropine (see *Warnings* and *Adverse Reactions* for anticholinergic side effects).

Pharmacokinetics: Following oral administration disopyramide phosphate is rapidly and almost completely absorbed, and peak plasma levels are usually attained within two hours. The usual therapeutic plasma levels of disopyramide *free base* are 2-4 mcg/ml and at these concentrations protein binding varies from 50-65%. Because of concentration-dependent protein binding, it is difficult to predict the concentration of the free drug when total drug is measured.

The mean plasma half-life of disopyramide in healthy humans is 6.7 hours (range of 4 to 10 hours). In six patients with impaired renal function (creatinine clearance less than 40 ml/min), disopyramide half-life values were 8 to 18 hours.

In healthy men about 50% of a given dose of disopyramide is excreted in the urine as the unchanged drug, about 20% as the mono-N-dealkylated metabolite and 10% as the other metabolites. The plasma concentration of the major metabolite is approximately one tenth that of disopyramide. Altering the urinary pH in man does not affect the plasma half-life of disopyramide.

INDICATIONS

Norpace should be prescribed only after appropriate electrocardiographic assessment.

Norpace (disopyramide phosphate) is indicated for suppression and prevention of recurrence of the following cardiac arrhythmias when they occur singly or in combination:

1. Unifocal premature (ectopic) ventricular contractions.
2. Premature (ectopic) ventricular contractions of multifocal origin.
3. Paired premature ventricular contractions (couplets).
4. Episodes of ventricular tachycardia (persistent ventricular tachycardia is ordinarily treated with D.C. cardioversion).

In controlled trials of ambulatory patients Norpace was as effective as 325 mg quinidine q 6 h in reducing the frequency of ventricular ectopic activity. Norpace was equally effective in digitalized and nondigitalized patients. Norpace is also equally effective in the treatment of primary cardiac arrhythmias and those which occur in association with organic heart disease including coronary artery disease.

Oral Norpace (disopyramide phosphate) has not been adequately studied in patients with acute myocardial infarction or in patients with persistent ventricular tachycardia or atrial arrhythmias.

Type 1 antiarrhythmic drugs are usually not effective in treating arrhythmias secondary to digitalis intoxication and, therefore, Norpace is not indicated for such cases.

The value of antiarrhythmic drugs in preventing sudden death in patients with serious ventricular ectopic activity has not been established.

CONTRAINDICATIONS

Norpace (disopyramide phosphate) is contraindicated in the presence of cardiogenic shock, preexisting second- or third-degree AV block (if no pacemaker is present), or known hypersensitivity to the drug.

WARNINGS

Negative inotropic properties: Heart failure/hypotension: **Norpace may cause or worsen congestive heart failure or produce severe hypotension as a consequence of its negative inotropic properties. Hypotension has been observed primarily in patients with primary cardiomyopathy or inadequately compensated congestive heart failure. Norpace should not be used in patients with uncompensated or marginally compensated congestive heart failure or hypotension unless the congestive heart failure or hypotension is secondary to cardiac arrhythmia. Patients with a history of heart failure may be treated with Norpace, but careful attention must be given to the maintenance of cardiac function, including optimal digitalization. If hypotension occurs or congestive heart failure worsens, Norpace should be discontinued and, if necessary, restarted at a lower dosage only after adequate cardiac compensation has been established.**

QRS widening: **Although it is unusual, significant widening (greater than 25%) of the QRS complex may occur during Norpace administration; in such cases Norpace (disopyramide phosphate) should be discontinued.**

Q-T prolongation: **As with other Type 1 antiarrhythmic drugs, prolongation of the Q-T interval (corrected) and worsening of the arrhythmia may occur. Patients who have evidenced prolongation of the Q-T interval in response to quinidine may be at particular risk. If a Q-T prolongation of greater than 25% is observed and if ectopy continues, the patient should be monitored closely, and consideration be given to discontinuing Norpace (disopyramide phosphate).**

Hypoglycemia: **In rare instances significant lowering of blood glucose values has been reported during Norpace administration.** The physician should be alert to this possibility, especially in patients with congestive heart failure, chronic malnutrition, hepatic, renal or other diseases or drugs (e.g., beta adrenoceptor blockers, alcohol) which could compromise preservation of the normal glucoregulatory mechanisms in the absence of food. In these patients the blood glucose levels should be carefully followed.

Concomitant antiarrhythmic therapy: **The concomitant use of Norpace with other Type 1 antiarrhythmic agents (such as quinidine or procainamide) and/or propranolol should be reserved for patients with life-threatening arrhythmias who are demonstrably unresponsive to single agent antiarrhythmic therapy. Such use may produce serious negative inotropic effects, or may excessively prolong conduction.** This should be considered particularly in patients with any degree of cardiac decompensation or those with a prior history thereof. Patients receiving more than one antiarrhythmic drug must be carefully monitored.

Heart block: **If first-degree heart block develops in a patient receiving Norpace, the dosage should be reduced.** If the block persists despite reduction of dosage, continuation of the drug must depend upon weighing the benefit being obtained against the risk of higher degrees of heart block. Development of second- or third-degree AV block or unifascicular, bifascicular or trifascicular block requires discontinuation of Norpace therapy, unless the ventricular rate is adequately controlled by a temporary or implanted ventricular pacemaker.

Anticholinergic activity: **Because of its anticholinergic activity, Norpace should not be used in patients with glaucoma, myasthenia gravis or urinary retention unless adequate overriding measures are taken;** these consist of the topical application of potent miotics (e.g., pilocarpine) for patients with glaucoma, and catheter drainage or operative relief for patients with urinary retention. Urinary retention may occur in patients of either sex as a consequence of Norpace administration, but males with benign prostatic hypertrophy are at particular risk. In patients with a family history of glaucoma, intraocular pressure should be measured before initiating Norpace therapy. Norpace should be used with special care in patients with myasthenia gravis since its anticholinergic properties could precipitate a myasthenic crisis in such patients.

PRECAUTIONS

Atrial tachyarrhythmias: Patients with atrial flutter or fibrillation should be digitalized prior to Norpace administration to ensure that drug-induced enhancement of AV conduction does not result in an increase of ventricular rate beyond physiologically acceptable limits.

Conduction abnormalities: Care should be taken when prescribing Norpace for patients with sick sinus syndrome (bradycardia-tachycardia syndrome), Wolff-Parkinson-White syndrome (WPW), or bundle branch block. The effect of Norpace (disopyramide phosphate) in these conditions is uncertain at present.

Cardiomyopathy: Patients with myocarditis or other cardiomyopathy may develop significant hypotension in response to the usual dosage of Norpace, probably due to cardiodepressant mechanisms. Therefore, a loading dose of Norpace should not be given to such patients and initial dosage and subsequent dosage adjustments should be made under close supervision (see *Dosage and Administration*).

Drug interactions: Other antiarrhythmic drugs (e.g., quinidine, procainamide, lidocaine, propranolol) have occasionally been used concurrently with Norpace but no specific drug interaction studies have been conducted (see *Warnings*). Excessive widening of the QRS complex and/or prolongation of the Q-T interval may occur in these situations. Norpace does not increase serum digoxin levels.

Renal impairment: More than 50% of disopyramide is excreted in the urine unchanged. Therefore Norpace dosage should be reduced in patients with impaired renal function (see *Dosage and Administration*). The electrocardiogram should be carefully monitored for prolongation of PR interval, evidence of QRS widening or other signs of overdosage (see *Overdosage*).

Hepatic impairment: Hepatic impairment also causes an increase in the plasma half-life of disopyramide. Dosage should be reduced for patients with such impairment. The electrocardiogram should be carefully monitored for signs of overdosage (see *Overdosage*).

Hypokalemia: Antiarrhythmic drugs may be ineffective in patients with hypokalemia. Therefore, any potassium deficit should be corrected before instituting Norpace (disopyramide phosphate) therapy.

Pregnancy: Reproduction studies in rats and teratology studies performed both in rats and in rabbits have revealed minimal evidence of impaired fertility. No fetal anomalies were attributable to Norpace. Disopyramide has been found in human fetal blood. However, well-controlled studies of Norpace have not been performed in pregnant women and experience with Norpace during pregnancy is limited; therefore the possibility of damage to the fetus cannot be excluded.

Norpace has been reported to stimulate contractions of the pregnant uterus. Norpace (disopyramide phosphate) should be used in pregnant women only when it is clearly indicated and the benefit/risk ratio has been carefully evaluated.

Labor and delivery: It is not known whether the use of Norpace during labor or delivery has immediate or delayed adverse effects on the fetus, or whether it prolongs the duration of labor or increases the need for forceps delivery or other obstetric intervention.

Nursing mothers: Studies in rats have shown that the concentration of disopyramide and its metabolites is between one and three times greater in milk than it is in plasma. Following oral administration, disopyramide has been detected in human milk at a concentration not exceeding that in plasma. Therefore, if use of the drug is deemed essential, an alternative method of infant feeding should be instituted.

Pediatrics: The safety and effectiveness of Norpace in children have not been established.

ADVERSE REACTIONS

The adverse reactions which were reported in clinical trials encompass observations in 1,500 patients, including 90 patients studied for at least four years. The most serious adverse reactions are hypotension and congestive heart failure. The most common adverse reactions, which are dose dependent, are associated with the anticholinergic properties of the drug. These may be transitory, but may be persistent or can be severe. Urinary retention is the most serious anticholinergic effect.

The following reactions were reported in 10-40% of patients:

Anticholinergic: dry mouth (32%), urinary hesitancy (14%), constipation (11%)

The following reactions were reported in 3-9% of patients:

Anticholinergic: blurred vision, dry nose/eyes/throat
Genitourinary: urinary frequency and urgency
Gastrointestinal: nausea, pain/bloating/gas
General: dizziness, general fatigue/muscle weakness, headache, malaise, aches/pains

The following reactions were reported in 1-3% of patients:

Anticholinergic: urinary retention
Genitourinary: impotence
Cardiovascular: hypotension with or without congestive heart failure, increased congestive heart failure (see *Warnings*), cardiac conduction disturbances (see *Warnings*), edema/weight gain, shortness of breath, syncope, chest pain
Gastrointestinal: anorexia, diarrhea, vomiting
Dermatologic: generalized rash/dermatoses, itching
Central nervous system: nervousness
Other: hypokalemia, elevated cholesterol/triglycerides

The following reactions were reported in less than 1%:

Depression, insomnia; dysuria; numbness/tingling; elevated liver enzymes; AV block; elevated BUN; elevated creatinine; decreased hemoglobin/hematocrit

Hypoglycemia has been reported in association with Norpace (disopyramide phosphate) administration (see *Warnings*).

Rarely, acute psychosis has been reported following Norpace therapy, with prompt return to normal mental status when therapy was stopped. Infrequent occurrences of reversible cholestatic jaundice have been reported in association with disopyramide therapy as have rare instances of reversible agranulocytosis. The physician should be aware of these possible reactions and should discontinue Norpace therapy promptly if they occur.

DOSAGE AND ADMINISTRATION

The dosage of Norpace (disopyramide phosphate) must be individualized for each patient on the basis of response and tolerance. The usual adult dosage of Norpace is 400 to 800 mg per day given in divided doses four times daily. The recommended dosage schedule for most adults is 150 mg every six hours. For patients whose body weight is less than 110 pounds (50 kg), the recommended dosage is 100 mg every six hours.

For patients with cardiomyopathy or possible cardiac decompensation, a loading dose, as discussed below, should not be given and initial dosage should be limited to 100 mg of Norpace every six hours. Subsequent dosage adjustments should be made gradually, with close monitoring for the possible development of hypotension and/or congestive heart failure (see *Warnings*).

For patients with moderate renal insufficiency (creatinine clearance greater than 40 ml/min) or hepatic insufficiency, Norpace dosage of 100 mg every six hours is recommended, with or without an initial loading dose of 200 mg.

For patients with severe renal insufficiency (C_{Cr} less than 40 ml/min) the recommended dosage regimen is an initial loading dose of 150 mg followed by a maintenance dose of 100 mg at intervals shown in the table below:

NORPACE DOSAGE INTERVAL FOR PATIENTS WITH RENAL INSUFFICIENCY

Creatinine clearance (ml/min)	40-30	30-15	less than 15
Approximate maintenance-dosing interval	q 8 hr	q 12 hr	q 24 hr

For patients in whom rapid control of ventricular arrhythmia is essential, an initial loading dose of 300 mg of Norpace (200 mg for patients whose body weight is less than 110 pounds) is recommended, followed by the appropriate maintenance dosage. Therapeutic effects are usually attained 30 minutes to three hours after administration of a 300-mg loading dose. If there is no response nor evidence of toxicity within six hours of the loading dose, 200 mg every six hours may be prescribed instead of the usual 150 mg. If there is no response to this dosage within 48 hours, either Norpace should then be discontinued or the physician should consider hospitalizing the patient for careful monitoring while subsequent doses of 250 or 300 mg every six hours are given. A limited number of patients with severe refractory ventricular tachycardia have tolerated daily doses of Norpace up to 1600 mg per day (400 mg every 6 hours) resulting in disopyramide plasma levels up to 9 mcg/ml. If such treatment is warranted, it is essential that patients be hospitalized for close evaluation and continuous monitoring.

Transferring to Norpace: The following dosage schedule based on theoretical considerations rather than experimental data is suggested for transferring patients with normal renal function from either quinidine sulfate or procainamide therapy (Type 1 antiarrhythmic agents) to Norpace therapy.

Norpace may be started using the regular maintenance schedule **without a loading dose** 6-12 hours after the last dose of quinidine sulfate or 3-6 hours after the last dose of procainamide.

In patients where withdrawal of quinidine sulfate or procainamide is likely to produce life-threatening arrhythmias, the physician should consider hospitalization of the patient.

OVERDOSAGE

No specific antidote for Norpace has been identified. Treatment of overdosage should be supportive and may include the administration of isoproterenol, dopamine, hemoperfusion with charcoal, hemodialysis, intra-aortic balloon counterpulsation and mechanically assisted respiration.

In vitro studies with human blood have demonstrated good dialyzability for disopyramide. Its clearance was 33 ml/min at a blood flow of 250 ml/min when an initial plasma concentration of 22 mcg/ml was dialyzed using an artificial kidney (Cordis-DOW-4).

On the basis of animal studies toxic plasma levels of disopyramide might be expected to produce excessive widening of the QRS complex and Q-T interval, worsening of congestive heart failure, hypotension, varying kinds and degrees of conduction disturbance, bradycardia and finally asystole. Obvious anticholinergic effects might also be observed. The electrocardiogram should be monitored and supportive therapy with vasopressors, sympathomimetics, cardiac glycosides and diuretics should be given as required.

HOW SUPPLIED

Norpace (disopyramide phosphate) is supplied in hard gelatin capsules containing either 100 mg or 150 mg of disopyramide base.

Norpace 100-mg capsules are white and orange, with markings SEARLE and 2752. Norpace 150-mg capsules are brown and orange, with markings SEARLE and 2762.

Available in bottles of 100, 500, and 1,000 capsules, and cartons of 100 unit-dose individually blister-sealed capsules.

SEARLE *Searle Laboratories*
Division of Searle Pharmaceuticals Inc.
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Adrenergic Regulation of Total Systemic Distensibility

Venous Distensibility Effects of Norepinephrine and Isoproterenol Before and After Selective Adrenergic Blockade

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The extracardiac factors that influence cardiac performance are arterial pressure and the venous return of blood to the heart. Venous return is influenced by the capacity and the distensibility characteristics of the peripheral capacitance vasculature. Distensibility determines the extent to which venous pressure increases and hence the extent to which venous return and cardiac performance increase when volume is added rapidly to the intravascular space. Thus an understanding of vascular distensibility is important to an understanding of integrated cardiovascular function. Because the influence of selective alpha and beta adrenergic receptor stimulation on total vascular distensibility is not well understood, the present study was undertaken to examine the distensibility effects of norepinephrine and isoproterenol before and after selective adrenergic receptor blockade. Fifty-one dogs were anesthetized, subjected to ganglionic block and placed on cardiopulmonary bypass at 1.5 liters/min. The reciprocal of distensibility or compliance was determined by sudden, transient occlusion of venous return and observation of the increase in central venous pressure (CVP) after a given amount of blood volume was added to the circulation (ΔCVP/83 ml). Norepinephrine, 30 μg/min, and isoproterenol, 6 μg/min, were each infused for 24 minutes. Norepinephrine was associated with an initial, transient (2 minute) increase in ΔCVP/83 ml of 18 $\pm$ 3 percent (mean $\pm$ standard error of the mean) ($p < 0.001$) above a control level of 16.9 $\pm$ 0.9 cm H_2O/83 ml, followed by a sustained decrease of 7 $\pm$ 3 percent ($p < 0.05$) below control level. Isoproterenol was associated with a decrease, which was both initial and sustained, in ΔCVP/83 ml of 19 $\pm$ 3 percent ($p < 0.001$) below a control level of 17.5 $\pm$ 1.0 cm H_2O/83 ml.

Selective blockade with phenoxybenzamine and propranolol revealed that the norepinephrine effect was mediated almost entirely through alpha adrenergic receptor stimulation and the isoproterenol effect mostly through beta adrenergic stimulation. Thus alpha and beta adrenergic receptor stimulation with norepinephrine and isoproterenol, respectively, is associated with sustained increases in total systemic vascular distensibility and would be expected to be associated with diminished increases in venous pressure, venous return and cardiac performance when a given amount of volume is added to the intravascular space.

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Cardiac performance is dependent on both systemic arterial resistance and venous return.[1] Venous return by means of the Frank-Starling mechanism is a major, if not the major, determinant of cardiac performance.[2–4] Venous return is dependent on both peripheral vascular capacity and the compliance or distensibility characteristics of the peripheral venous circulation. Changes in systemic vascular capacity result in translocations of intravascular volume between the central (heart and lungs) and peripheral circulations. Distensibility is related to the extent by which venous pressure is altered and subsequently venous return and

cardiac output are altered when volume is added to or removed from the venous circulation. For example, if volume is added to the venous circulation at a given venous pressure and capacity, venous vascular distensibility determines the extent by which venous pressure increases. The extent by which venous pressure increases determines the magnitude of the increase in venous return. The magnitude of the increment in venous return, through the Frank-Starling mechanism, determines the extent by which cardiac performance is increased. Thus the distensibility of the venous circulation is a very important factor in overall circulatory function during intravenous volume repletion.

Little is known about the effects of adrenergic agents on total venous distensibility. Alexander[5] examined the effects of phenylephrine and epinephrine in an isolated mesenteric vein preparation. He found that at higher venous distending pressures, the administration of either of these agents was associated with an increase in venous distensibility. At lower distending pressures, he noted no change in distensibility. Ross et al.[6] assessed the effects of norepinephrine and epinephrine on venous distensibility in the total animal. They found that norepinephrine and epinephrine were both associated with increases in vascular distensibility at a single control level of venous pressure. However, they did not assess the possibility that the level of central venous pressure might modulate the effect of catecholamines on total vascular distensibility, as suggested by the work of Alexander. Furthermore, neither study examined the effect of selective alpha or beta adrenergic receptor stimulation on total venous distensibility. It is important for the clinician to have a basic understanding of the selective effects of alpha and beta adrenergic receptor stimulation on venous distensibility when a sympathomimetic drug is selected for therapeutic intervention. For example, if alpha or beta adrenergic receptor stimulation increases vascular distensibility, it would be expected that venous pressure and venous return would increase less with intravenous volume repletion in the presence of an alpha or beta adrenergic agent than if that agent were absent.

Thus the present study assessed the effects of alpha and beta adrenergic receptor stimulation on total systemic distensibility by employing norepinephrine and isoproterenol, two commonly utilized clinical agents, both before and after selective adrenergic receptor blockade. The effects of these agents on distensibility over a range of central venous pressures were examined. The model employed was a canine cardiopulmonary bypass preparation in which a change in pressure in the systemic venous vasculature could be determined as a function of the volume added to the systemic vasculature.

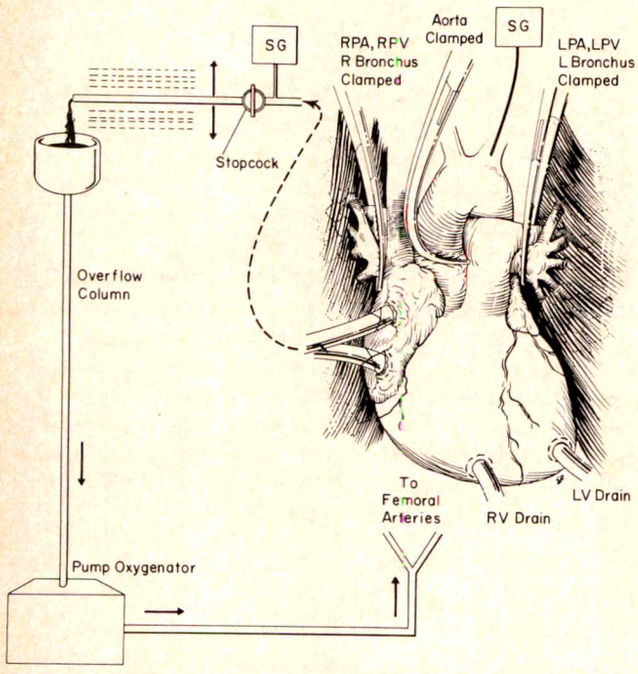

FIGURE 1. Experimental preparation. Dogs were placed on total cardiopulmonary bypass. Intermittent venous occlusions were accomplished by turning the stopcock. See text for details. LPA = left pulmonary artery; LPV = left pulmonary vein; LV = left ventricle; RPA = right pulmonary artery; RPV = right pulmonary vein; RV = right ventricle; SG = strain gauge.

Methods

Experimental Preparation (Fig. 1)

Fifty-one dogs weighing 17 to 25 kg were anesthetized with chloralose (60 mg/kg intravenously) and urethane (600 mg/kg intravenously). After tracheal intubation, respiration was achieved with a Harvard respirator using 97 percent oxygen/3 percent carbon dioxide. A median sternotomy was performed and 3 mg/kg of heparin was administered intravenously. The azygos vein was ligated. Total venous return to the reservoir of a pump oxygenator was accomplished by cannulating the superior and inferior venae cavae through the right atrial appendage with Argyle 32 French catheters. A 90° rotation of a stopcock (internal diameter 12 mm) produced rapid and complete occlusion of the systemic venous drainage tubing (internal diameter 13 mm). Central venous pressure was measured in the venous return line between the stopcock and the animal and was set at a predetermined level by adjusting the height of a venous overflow column. The roller pump (Cardiovascular Instruments, Wakefield, Massachusetts), returning oxygenated blood to the femoral arteries of the dog, was set at 1.5 liters/min. Blood was oxygenated using a Harvey model H-1000 oxygenator (William Harvey, Santa Ana, California). Arterial pressure was measured through a cannula in the subclavian artery. The aorta was cross-clamped 2 cm above the aortic valve, and the pulmonary hila were clamped to exclude the coronary, pulmonary and bronchial circulation. Hence any contribution of the cardiac chambers or pulmonary vasculature to total systemic compliance was excluded. The adequacy of clamping was demonstrated by the absence of flow from drains placed in both ventricles. All pressures were monitored using Statham

P23Db pressure transducers; the frequency response of the pressure measurement system was linear up to 30 cycles/s. Pressures were recorded on a Hewlett-Packard model 7700 eight-channel recorder at a paper speed of 25 mm/s.

Assessment of systemic distensibility and compliance: In order to assess total systemic distensibility or compliance, the stopcock was rapidly turned to the closed position, and central venous pressure was allowed to increase for more than 3.3 seconds. The stopcock was then rapidly turned to the open position, and central venous pressure promptly decreased toward its preocclusion level. Because the output of the roller pump was constant, the volume of blood pumped per unit of time was known. Hence it was possible to ascertain the change in pressure per unit of volume pumped into the systemic vasculature, that is, the inverse of distensibility or compliance. We recognize that the total systemic capacitance vasculature is composed of several separate components arranged in parallel.[7–10] Distensibility in any one of these components may be altered passively by changes in resistance to inflow to that component or by active vasoconstriction or dilation in that component. The present model allows an assessment of overall vascular distensibility in all components of the capacitance vasculature.

In preliminary studies we observed that with different interventions, the initial rate of increase of central venous pressure as a function of volume pumped was proportional to the change in pressure several seconds after occlusion. It was found that the appropriate time to measure the change in central venous pressure at a perfusion rate of 1.5 liters/min was 3.3 seconds after venous occlusion when 83 ml had been pumped (Fig. 2). At this point changes in the increase in central venous pressure produced by drug infusion could easily be noted, and at this time pressure never exceeded 35 mm Hg. It might be argued that 3.3 seconds is an insufficient period for venous pressure to be transmitted in retrograde fashion to the small veins and postcapillary venules where the major portion of the intravascular volume is located. Thus, measuring the change in central venous pressure after such a relatively brief period might not allow an adequate assessment of compliance. However, a pressure increment has been transmitted in retrograde manner to such an extent by 3.3 seconds that arterial pressure has increased slightly (Fig. 2). Thus, the change in venous pressure when 83 ml of infusate has been pumped (ΔCVP/83 ml) is a reasonable assessment of total systemic distensibility.

Ganglionic blockade was produced by the administration of 100 mg of mecamylamine (Inversine®, Merck, Sharpe & Dohme, West Point, Pennsylvania) to the pump reservoir over 10 minutes. This dose was adequate to abolish entirely 50 mm Hg increases in perfusion pressure obtained by clamping a single carotid artery below the bifurcation in preliminary experiments. Bilateral cervical vagectomy was also performed.

Adrenergic Receptor Regulation

Isoproterenol (Isuprel®, Winthrop Laboratories, New York, New York), 6 μg/min, norepinephrine (Levophed®, Winthrop Laboratories), 30 μg/min and methoxamine (Vasoxyl®, Burroughs Wellcome Co., Research Triangle Park, North Carolina), 200 or 400 μg/min, were each infused with a parenteral Fluid Delivery System (IV 5000, Valleylab, Boulder, Colorado). Each drug was dissolved in normal saline solution at concentrations that allowed infusion of the solutions at 2 ml/min. Alpha and beta adrenergic receptor blockade was achieved with phenoxybenzamine (Dibenzyline®, Smith, Kline & French Laboratories, Philadelphia, Pennsylvania), 0.1 to 2.0 g, and propranolol (Inderal®, Ayerst Laboratories, New York, New York), 20 to 200 mg, administered intravenously. Pharmacologic blockade was assessed by noting systemic arterial pressure responses to bolus injections of 300 μg of phenylephrine (Neosynephrine®, Winthrop Laboratories) and 12 μg of isoproterenol administered intraarterially before and after blockade. Arterial pressure responses with these agents were abolished before and after each experimental infusion administered in the presence of alpha or beta adrenergic blockade.

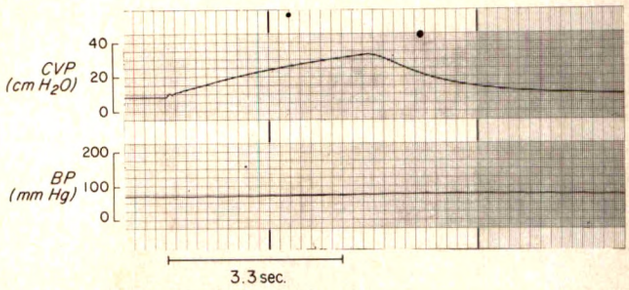

FIGURE 2. Representative tracing of central venous pressure (CVP) and arterial pressure (BP) before, during and after venous occlusion. Venous return to the reservoir was occluded at the beginning of the 3.3 second period. Central venous pressure after venous occlusion had not quite returned to the control level in this tracing, but it did so by 2 minutes.

Norepinephrine and isoproterenol infusions: In 31 animals, norepinephrine or isoproterenol, or both, was administered for 24 minutes. Venous occlusions were performed every 2 minutes during each infusion and during control periods before and after each infusion, except for the first 2 minutes of drug administration, when occlusions were performed every 30 seconds. The drugs were administered in a random fashion and were infused before and after selective alpha or beta adrenergic receptor blockade or double blockade. Normal saline solution alone was infused at 2 ml/min in four of these animals, and venous occlusions were performed before and during the infusion as described earlier. In two other animals, norepinephrine was infused at 3.75, 7.5 and 15 μg/min for 24 minutes but at concentrations that still allowed infusion rates of 2 ml/min. Splenectomy was performed in five other animals to eliminate the contractile effect of norepinephrine on the muscular capsule of the spleen.[11,12] In these animals, norepinephrine was infused on seven occasions at 30 μg/min for 24 minutes. In two other animals

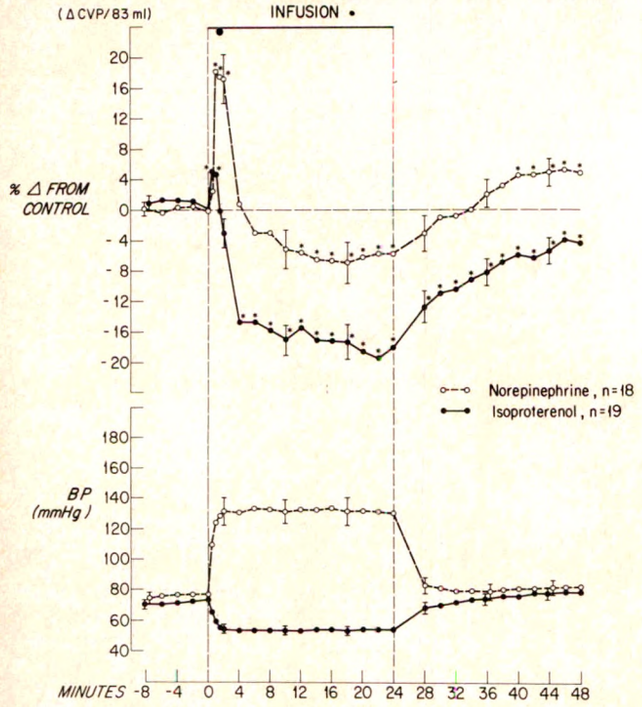

FIGURE 3. Change in central venous pressure (CVP) after 83 ml of infusate had been pumped (ΔCVP/83 ml) and arterial pressure (BP) during norepinephrine and isoproterenol infusion. Norepinephrine was infused at 30 μg/min and isoproterenol at 6 μg/min. Each **bar** represents ± 1 standard error of the mean. **Asterisks** indicate statistical significance ($p < 0.05$) compared with the preinfusion control values.

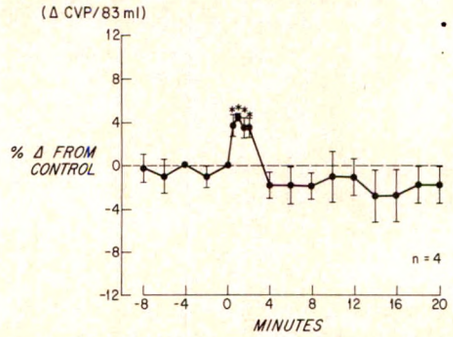

FIGURE 4. ΔCVP/83 ml during infusion of normal saline solution at 2 ml/min from time 0 to 20 minutes. Symbols and abbreviations as in Figure 3.

without splenectomy, methoxamine was infused on three occasions at 200 or 400 μg/min for 24 minutes.

In 11 animals, the effect of norepinephrine and isoproterenol infusions on the response to venous occlusion was assessed at central venous pressures of 3, 8 and 13 cm H_2O. In these experiments, venous occlusions were performed at these three venous pressures before each infusion of norepinephrine or isoproterenol, just before the termination of each infusion and at 10 minute intervals for 30 minutes after each infusion. At least 2 minutes of equilibration was allowed whenever venous pressure was altered. Central venous pressure was maintained at 3 cm H_2O between each set of venous occlusions. In these experiments norepinephrine and isoproterenol were administered for 15 and 10 minutes, respectively.

Statistical analysis: For each infusion, the percent change from the value of the ΔCVP/83 ml immediately before drug administration was determined for each value of ΔCVP/83 ml. Means were computed for the percent changes at each point in time for all experiments in each experimental group. A double-tailed Student's *t* test was then performed on all means in each group to ascertain whether the changes were statistically significant. Significance was assumed only with probability (p) values less than 0.05.

Results

Effects of isoproterenol and norepinephrine infusion (Fig. 3): Isoproterenol was associated with a transient initial increase in central venous pressure when 83 ml of infusate had been pumped (ΔCVP/83 ml) of only 5 ± 1 percent (mean ± standard error of the mean) ($p < 0.001$) above a control level of 17.5 ± 1.0 cm H_2O/83 ml, which lasted only 1 minute from the onset of infusion; ΔCVP/83 ml then decreased. This decrease persisted for the duration of the infusion and reached a minimum of 19 ± 3 percent ($p < 0.001$) below control. Thus isoproterenol was associated with a sustained increase in distensibility.

Norepinephrine administration was associated with an initial increase in ΔCVP/83 ml of 18 ± 3 percent ($p < 0.001$) above a control level of 16.9 ± 0.9 cm H_2O/83 ml; ΔCVP/83 ml then decreased. This decrease persisted for the duration of the infusion and reached a minimum of 7 ± 3 percent ($p < 0.05$) below the control value. Thus, norepinephrine was associated with an initial decrease followed by a sustained increase in distensibility. During the last 8 minutes of the postnorepinephrine control period, ΔCVP/83 ml was significantly increased above the control level. In the nine animals in which norepinephrine was administered without a previous infusion of isoproterenol, the sustained decrease in ΔCVP/83 ml during norepinephrine was similar to that in Figure 3, and ΔCVP/83 ml returned to, but not above, control levels after termination of the infusion. Thus the mean increase in ΔCVP/83 ml during the postnorepinephrine period in Figure 3 was probably due to a persistent isoproterenol effect lowering ΔCVP/83 ml before norepinephrine infusion in the animals that received isoproterenol before norepinephrine. Note that arterial pressure rapidly increased to a peak and remained at that level for the duration of norepinephrine administration.

When venous occlusions were performed during infusion of normal saline solution at the same intervals as those in Figure 3, ΔCVP/83 ml increased significantly to 5 percent above the control value during the first 2 minutes of the infusions (Fig. 4). This increase during saline infusion was probably due to an inadequate period of time for blood to leave the capacitance vasculature between occlusions, which were performed every 30 seconds during the first 2 minutes of the infusions. Thus the initial increase in ΔCVP/83 ml with norepinephrine was more than could be accounted for by the

TABLE 1.

Compliance Changes With Small Dose Administration of Norepinephrine

	Control	2 min	4 min	8 min	24 min
3.75 μg/min of Norepinephrine					
ΔCVP/83 ml*	23 cm H_2O	+4%	−4%	−4%	−9%
BP (mm Hg)	95	100	95	95	95
ΔCVP/83 ml†	25 cm H_2O	+4%	−4%	−8%	−8%
BP (mm Hg)	105	120	120	120	115
7.5 μg/min of Norepinephrine					
ΔCVP/83 ml*	22 cm H_2O	+14%	0%	−5%	−9%
BP (mm Hg)	80	110	110	110	110
ΔCVP/83 ml*	18 cm H_2O	+11%	0%	−6%	−6%
BP (mm Hg)	90	110	110	110	105
ΔCVP/83 ml†	26 cm H_2O	+12%	0%	−4%	−12%
BP (mm Hg)	90	120	115	115	115
15 μg/min of Norepinephrine					
ΔCVP/83 ml*	21 cm H_2O	+5%	−10%	−14%	−19%
BP (mm Hg)	90	115	115	115	115
ΔCVP/83 ml*	22 cm H_2O	+27%	+9%	−9%	−14%
BP (mm Hg)	70	110	105	105	100
ΔCVP/83 ml†	24 cm H_2O	0%	−8%	−12%	−12%
BP (mm Hg)	95	135	135	130	125

* Animal 1. † Animal 2.

The control value for ΔCVP/83 ml is expressed as an absolute value. Subsequent values of ΔCVP/83 ml during each infusion are expressed as percent changes compared with the control value. BP = arterial pressure; CVP = central venous pressure.

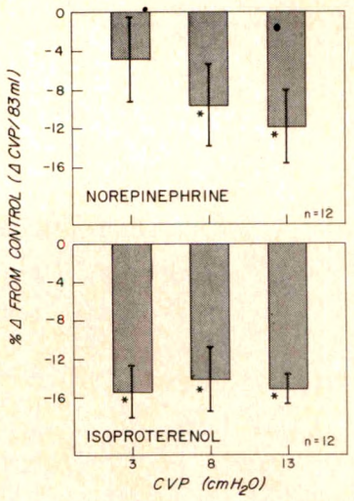

FIGURE 5. Effects of norepinephrine and isoproterenol on ΔCVP/83 ml at three levels of central venous pressure (CVP). Norepinephrine was infused for 15 minutes at 30 μg/min and isoproterenol for 10 minutes at 6 μg/min. Symbols and abbreviations as in Figure 3.

technique alone, whereas the initial increase with isoproterenol appeared secondary to the frequent clamping.

The hemodynamic changes associated with 24 minutes of norepinephrine infusion at concentrations less than 30 μg/min are shown in Table I. Note that except for the absence of an initial increase in ΔCVP/83 ml during some of the infusions, the changes are directionally similar to those in Figure 3.

In the five splenectomized animals, norepinephrine at a concentration of 30 μg/min was associated with an initial increase in ΔCVP/83 ml of 11 ± 3 percent ($p < 0.01$) above a control level of 21 ± 1 cm H_2O/83 ml. This initial increase was greater than that produced by the technique alone (Fig. 4). ΔCVP/83 ml subsequently decreased to 14 ± 2 percent ($p < 0.001$) below control after 24 minutes of norepinephrine infusion in these splenectomized animals.

Changes in venous distensibility (ΔCVP/83 ml) at various levels of central venous pressure (Fig. 5): The administration of norepinephrine did not produce a significant decrease in ΔCVP/83 ml at a central venous pressure of 3 cm H_2O. At this pressure, ΔCVP/83 ml was actually increased at the end of the 15 minute norepinephrine infusion on three occasions, unchanged on another three occasions and decreased at the end of the other six infusions. Norepinephrine administration at central venous pressures of 8 and 13 cm H_2O and isoproterenol administration at all three pressure levels examined revealed significant decreases in ΔCVP/83 ml at the end of the infusions. Control values of ΔCVP/83 ml were 9.9 ± 2.6, 10.5 ± 2.7 and 11.4 ± 2.9 cm H_2O/83 ml at central venous pressures of 3, 8 and 13 cm H_2O, respectively, for norepinephrine infusion and 11.2 ± 3.5, 10.7 ± 2.4 and 11.1 ± 2.4 cm H_2O/83 ml for isoproterenol infusion. The different durations of infusion for norepinephrine (15 minutes) and isoproterenol (10 minutes) were chosen because decreases in ΔCVP/83 ml had reached levels that were relatively stable and significantly below the control value by 15 minutes with norepinephrine and by 10 minutes with isoproterenol (Fig. 3). In two animals in which norepinephrine and isoproterenol were each infused twice at a central venous pressure of 8 cm H_2O, no attenuation of the changes in ΔCVP/83 ml occurred during the second infusion of each drug.

Effects of alpha and beta adrenergic receptor blockade with phenoxybenzamine or propranolol: The effects of norepinephrine after administration of either 100 mg of phenoxybenzamine or 20 mg of propranolol were studied (Fig. 6). After 20 mg of propranolol, the sustained decrease in ΔCVP/83 ml was minimally but not significantly attenuated. After 100 mg of phenoxybenzamine alone, the initial increase in ΔCVP/83 ml was the same as without alpha adrenergic receptor blockade, but the sustained decrease in ΔCVP/83 ml was abolished. In these experiments with norepinephrine administration after 100 mg of phenoxybenzamine, the initial increase in ΔCVP/83 ml was associated with a small and transient but steep increase in arterial pressure, suggesting the possibility that alpha adrenergic blockade was not complete. In two other animals, alpha adrenergic receptor blockade with a larger dose of phenoxybenzamine (2 g) abolished both the norepinephrine-associated initial increase and the subsequent sustained decrease in ΔCVP/83 ml.

Whenever norepinephrine was infused, there was an initial steep increase followed by a plateau or slight

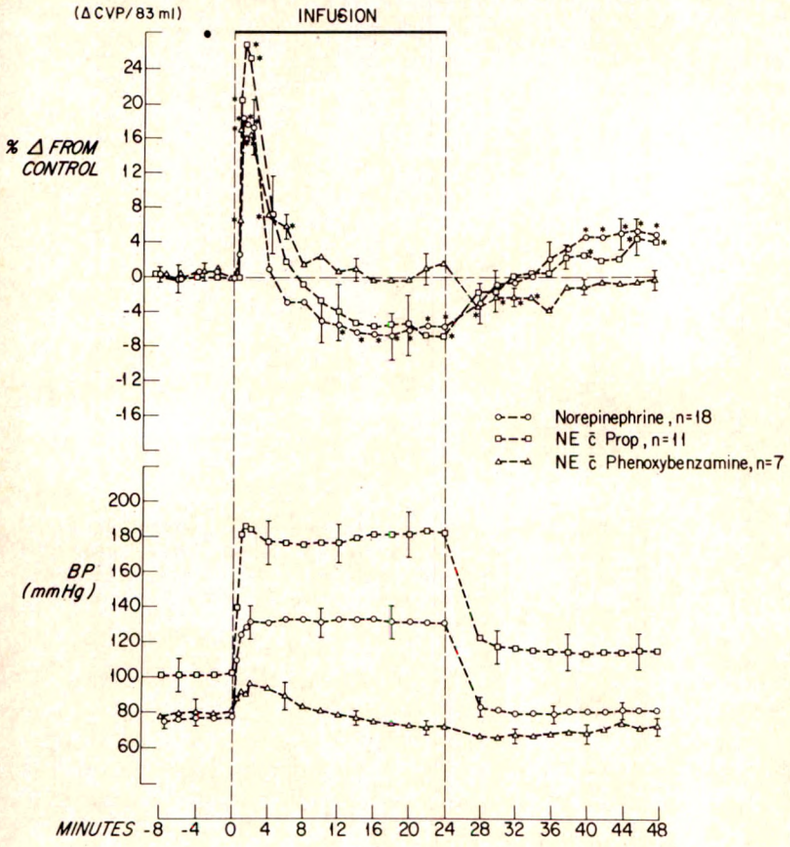

FIGURE 6. Effect of norepinephrine, 30 μg/min, without adrenergic blockade, and after blockade with either 20 mg of propranolol or 100 mg of phenoxybenzamine. The data associated with administration of norepinephrine (NE) in the absence of adrenergic blockade are reproduced from Figure 3. Note that the norepinephrine-associated decrease in ΔCVP/83 ml was abolished after alpha adrenergic blockade and was slightly but not significantly attenuated after beta adrenergic blockade. Control ΔCVP/83 ml was 16.9 ± 0.9 cm H_2O/83 ml before blockade, 17.9 ± 1.3 after alpha adrenergic blockade and 21.0 ± 1.2 after beta adrenergic blockade. Symbols and abbreviations as in Figure 3.

decrease in blood pressure. This initial increase in blood pressure was always associated with a transient increase in ΔCVP/83 ml. This association suggested the possibility that a progressive vasoconstrictor effect, albeit transient in these experiments, is associated with an increase in ΔCVP/83 ml. In this regard it was noted that when methoxamine was infused there was a progressive increase in arterial pressure (Fig. 7) throughout the duration of the the infusion (three infusions in two animals). In these experiments, ΔCVP/83 ml did not decrease below the control level and actually increased progressively in two infusions (Fig. 7).

The isoproterenol-associated decrease in ΔCVP/83 ml was attenuated after individual blockade with either 20 mg of propranolol or 100 mg of phenoxybenzamine (Fig. 8). After double blockade with these doses of both of the blocking agents, ΔCVP/83 ml still decreased slightly, although not significantly. Phenoxybenzamine (1 g) produced no further attenuation of the isoproterenol-associated decrease in ΔCVP/83 ml than had 100 mg phenoxybenzamine (Fig. 9). Subsequent double blockade with large dose propranolol (200 mg) and 1 g of phenoxybenzamine abolished the decrease in ΔCVP/83 ml. Beta adrenergic receptor blockade alone with larger dose (200 mg) propranolol almost but not entirely abolished the isoproterenol-associated decrease in ΔCVP/83 ml (Fig. 10). Subsequent double blockade by the addition of 1 g of phenoxybenzamine entirely abolished the decrease. In two animals, 300 μg of phenylephrine administered intraarterially was associated with respective increases in arterial pressure of 32 and 29 mm Hg before 200 mg of propranolol and increases of 33 and 30 mm Hg after 200 mg of propranolol. Thus it is unlikely that this dose of propranolol produced any alpha adrenergic receptor blockade.

Discussion

Effects of alpha and beta adrenergic stimulation on vascular capacity and distensibility: The present study demonstrates the influence of norepinephrine and isoproterenol on the distensibility or compliance characteristics of the peripheral capacitance vasculature. The data indicate that the administration of both norepinephrine and isoproterenol results in sustained increases in vascular distensibility; that is, when a given amount of volume is added to the circulation, venous pressure will increase less in the presence of either of these agents than in its absence. The data also demonstrate that the distensibility effects of norepinephrine and isoproterenol are mediated through alpha and beta adrenergic receptor stimulation, respectively.

It must be remembered that alpha and beta adrenergic receptor stimulation affects both vascular capacity and vascular distensibility. Previous work has demonstrated that such stimulation decreases total systemic vascular capacity.[13,14] This change in capacity occurs relatively rapidly (10 to 15 minutes) and is associated with a new steady state peripheral systemic

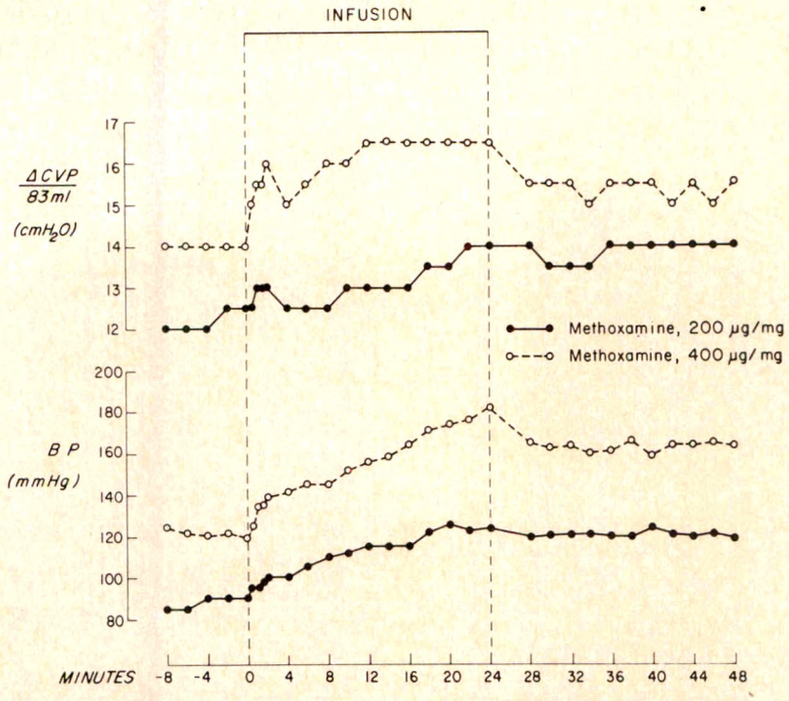

FIGURE 7. ΔCVP/83 ml and arterial pressure during infusions of methoxamine at two different doses. Small dose methoxamine was infused first. Note that arterial pressure continued to increase and ΔCVP/83 ml remained increased above control for the duration of each infusion. ΔCVP/83 ml is expressed as an absolute value. Abbreviations as in Figure 3.

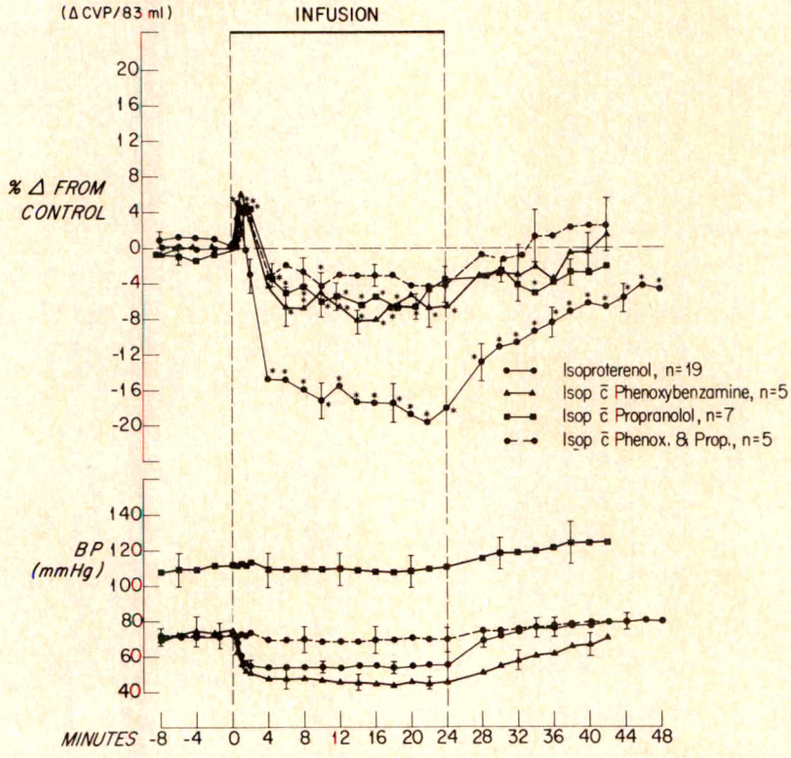

FIGURE 8. Effect of isoproterenol (Isop), 6 μg/min, without adrenergic blockade and after blockade with either 20 mg of propranolol (Prop.) or 100 mg of phenoxybenzamine (Phenox.) or after double blockade with both agents. The data associated with isoproterenol administration in the absence of adrenergic blockade are reproduced from Figure 3. Note that the isoproterenol-associated decrease in ΔCVP/83 ml was attenuated after either alpha or beta adrenergic blockade. After subsequent double blockade, ΔCVP/83 ml decreased a small but not statistically significant amount. Control ΔCVP/83 ml was 17.5 ± 1.0 cm H_2O/83 ml before blockade, 16.8 ± 2.0 after alpha adrenergic blockade, 20.4 ± 1.6 after beta adrenergic blockade and 19.0 ± 1.3 after double blockade. Symbols and abbreviations as in Figure 3.

intravascular volume. Under these steady state conditions, the change in peripheral capacity due to selective adrenergic receptor stimulation has already been manifested, and subsequent influences of adrenergic receptor stimulation on the capacitance circulation will be manifested as changes in vascular distensibility. Specifically, the influences will be apparent in terms of the extent to which the change in venous pressure, with volume repletion or depletion, is altered. The present data demonstrate that alpha and beta adrenergic stimulation is associated with significant sustained increases in vascular distensibility. Thus, once systemic vascular capacity has decreased secondary to adrenergic receptor stimulation, changes in venous pressure, resulting from subsequent repletion or depletion of the intravascular space, would be much smaller in the presence of alpha or beta receptor stimulation. For that reason, changes in venous return and cardiac output, after altering intravascular volume, would be attenuated during such stimulation.

Effects of norepinephrine: Norepinephrine administration is associated with an initial decrease in

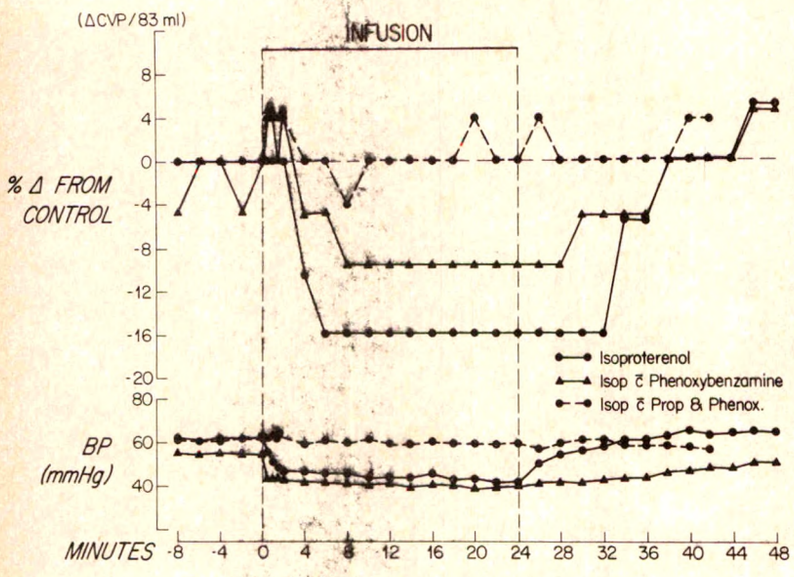

FIGURE 9. Effect of isoproterenol (Isop), 6 μg/min, in a single animal before blockade, after 1 g of phenoxybenzamine (Phenox.) and after double blockade with the subsequent administration of 200 mg of propranolol (Prop). Note that the isoproterenol-associated decrease in ΔCVP/83 ml was attenuated approximately the same amount with 1 g of phenoxybenzamine as it had been with 100 mg of phenoxybenzamine (Fig. 8). Control ΔCVP/83 ml was 9.5 cm H_2O/83 ml before blockade, 10.5 after alpha adrenergic blockade and 12.5 after double blockade. Abbreviations as in Figure 3.

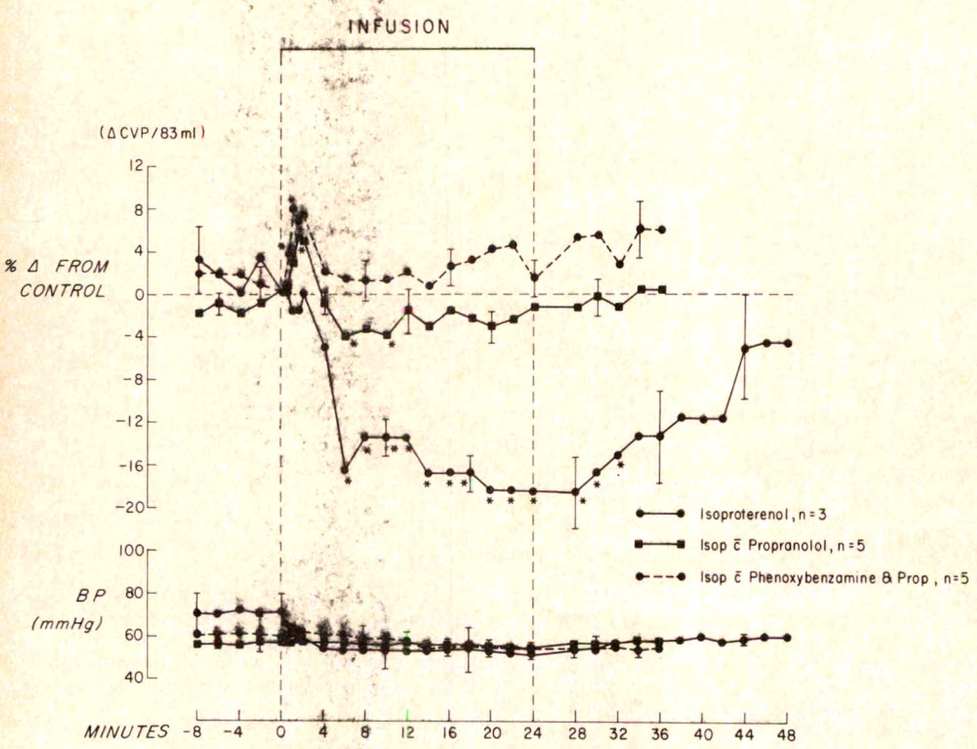

FIGURE 10. Effect of isoproterenol (Isop), 6 μg/min, before blockade, after 200 mg of propranolol (Prop) and after double blockade with the subsequent administration of 1 g of phenoxybenzamine. Note that the isoproterenol-associated decrease in ΔCVP/83 ml was almost but not entirely abolished after 200 mg of propranolol. With the subsequent addition of phenoxybenzamine, the isoproterenol-associated decrease in ΔCVP/83 ml was abolished. Control ΔCVP/83 ml was 10.0 ± 0.3 cm H_2O/83 ml before blockade, 10.3 ± 1.1 after beta adrenergic blockade and 10.6 ± 1.7 after double blockade. Symbols and abbreviations as in Figure 3.

total systemic distensibility. The decrease is mediated entirely through alpha adrenergic receptor stimulation as it is abolished after large dose alpha adrenergic blockade with phenoxybenzamine. It might be argued that the initial decrease in compliance with norepinephrine is due to a lower serum drug concentration during the initial period of infusion and the later sustained increase in distensibility is due to the subsequent development of a higher serum drug concentration. That this is not so is demonstrated by the lack of a prolonged decrease in distensibility even at lower levels of drug delivery (Table I). The initial decrease in distensibility may be related to the presence of progressive vasoconstriction because the decrease is manifest only while arterial pressure is increasing. In support of this argument is the observation that, for the duration of methoxamine administration, distensibility does not increase and either steadily decreases or remains constant while arterial pressure steadily increases. Thus it appears likely that progressively increasing alpha adrenergic receptor stimulation may be associated with a decrease in venous distensibility; that is, administration of a given amount of volume would result in a higher venous pressure during progressively increasing alpha adrenergic receptor stimulation than before stimulation.

However, once arterial pressure has stabilized with norepinephrine administration, systemic distensibility increases and eventually reaches a level significantly above the control value. Distensibility remains at this higher level for the duration of drug administration. This increase in distensibility with norepinephrine is mediated almost entirely through alpha adrenergic receptor stimulation, as the increase is abolished after pharmacologic blockade of alpha adrenergic receptors. It is possible that a small portion of the distensibility-increasing effect of norepinephrine is mediated through beta adrenergic receptor stimulation, because the increase in distensibility with norepinephrine is slightly but not significantly attenuated after beta adrenergic receptor blockade with propranolol. The importance of central venous pressure in modulating the influence of adrenergic agents on systemic distensibility is indicated by the observation that the sustained increase in distensibility with norepinephrine occurs only at higher central venous pressures. Neither the decrease nor the increase in distensibility associated with norepinephrine administration is mediated entirely through splenic constriction, as the bimodal pattern of response is still present in animals that have undergone splenectomy.

Effects of isoproterenol: Isoproterenol is associated with a marked increase in distensibility over a wide range of central venous pressures. This isoproterenol-associated increase appears predominantly related to beta adrenergic receptor stimulation, as the increase in distensibility is nearly eliminated after beta adrenergic receptor blockade with 200 mg of propranolol. It is unlikely that this dose of propranolol causes any substantial alpha adrenergic receptor blockade, because phenylephrine-associated increases in arterial pressure are not attenuated by this dose of propranolol. However, a small portion of the isoproterenol-associated increase in distensibility, is likely to be mediated through alpha adrenergic receptor stimulation for the following reasons: The isoproterenol effect on distensibility is present to a limited extent after blockade with 200 mg of propranolol alone, is entirely abolished after subsequent double blockade with propranolol and phenoxybenzamine, and is attenuated after blockade with 100 mg of phenoxybenzamine alone. The apparent attenuation by one half of the isoproterenol-associated increase in distensibility after 100 mg of phenoxybenzamine does not necessarily imply that isoproterenol exerts its effect to such a large extent through alpha adrenergic receptor stimulation. The attenuation may be related in part to shifts along the steady state pressure/volume curve caused by phenoxybenzamine. These shifts may affect the physical characteristics of the vasculature such that after phenoxybenzamine, the control level of distensibility does not change, but with subsequent isoproterenol administration, an apparent attenuation of the isoproterenol effect is manifest. Stimulation of both alpha and beta adrenergic receptors by isoproterenol is not totally unexpected, because recent in vitro studies suggest some affinity of isoproterenol for the alpha adrenergic receptor.[15]

Previous studies on vascular compliance or distensibility: Alexander,[5] employing an isolated mesenteric vein preparation, measured the increase in mesenteric vein pressure with volume infusion. He noted that phenylephrine administration was associated with an increase in compliance or distensibility at higher initial distending pressures but no change in compliance at lower distending pressures. In our study we noted sustained increases in total systemic compliance or distensibility with norepinephrine at central venous pressures of 8 and 13 cm H_2O but no significant change in total distensibility at a central venous pressure of 3 cm H_2O. Thus our results extend the observations of Alexander to the total systemic capacitance vasculature.

Ross et al.,[6] employing an animal preparation similar to ours, found that norepinephrine and epinephrine both produced increases in systemic compliance. However, norepinephrine and epinephrine are associated with both alpha and beta adrenergic stimulatory effects in the overall circulatory system. Because Ross et al. did not employ selective adrenergic receptor blockade, they could not ascertain whether the increases in compliance were due to alpha or beta adrenergic receptor stimulation or to both. Furthermore, they could not eliminate the possible contribution of peripheral or central baroreceptors to the catecholamine-associated effects, since they did not administer ganglionic blockade before catecholamine infusion as was done in our study.

Caldini et al.[7] and Mitzner and Goldberg[8] assessed intravascular compliance by noting changes in total intravascular volume associated with increments in right atrial pressure or changes in regional mean venous pressure associated with increments in regional intravascular volume. They found epinephrine to be associated with decreases in total and regional intravascular capacitance. However, they did not determine whether

the decrease in capacitance was due to alpha or beta adrenergic receptor stimulation, or both. It is possible that epinephrine produced progressive alpha adrenergic-mediated venoconstriction of the capacitance vasculature similar to that we observed during the initial period of norepinephrine infusion or throughout the period of methoxamine infusion. Furthermore, they did not eliminate the possible contribution of central or peripheral baroreceptors.

Clinical implications: In addition to a better understanding of overall circulatory function, this study contributes to our understanding of cardiocirculatory function associated with such pathophysiologic states as congestive heart failure and to our knowledge of the therapeutic implications of sympathomimetic drug administration. It is well known that sympathetic tone is increased in the presence of congestive heart failure.[16–19] This elevation might be beneficial to the patient in that venous pressure would be expected to be increased much less for a given increment in vascular volume. Such attenuation would tend to protect the patient from central volume overload, which could produce pulmonary edema or ascites. However, much more volume would have to be removed from the intravascular space in order to decrease ventricular filling pressures. Thus the treatment of pulmonary edema or ascites might become more difficult. Similarly, in the presence of sympathomimetic drug administration, more volume would have to be administered intravenously in order to increase venous return and cardiac output, and a greater amount of volume would have to be removed in order to lower venous pressure. Because our work has assessed the influences of selective alpha and beta adrenergic receptor stimulation, the study should allow prediction of the distensibility effects of many adrenergic agents. Under steady state conditions and in the absence of progressive vasoconstriction, alpha and beta adrenergic agents would both be expected to be associated with increases in vascular distensibility. However, agents with more alpha adrenergic effects would tend to have smaller distensibility effects at low central venous pressures.

Acknowledgment

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Production of a Critical Coronary Arterial Stenosis in Closed Chest Laboratory Animals

Description of a New Nonsurgical Method Based on Standard Cardiac Catheterization Techniques

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A nonsurgical method for producing a critical coronary arterial stenosis in a closed chest laboratory animal would enhance our ability to study the effects of reversible myocardial ischemia on many aspects of left ventricular function and also would facilitate experiments aimed at studying the effects of various interventions on regional myocardial blood flow distal to a severe stenosis. Accordingly, a new technique was developed for the production of a critical coronary arterial lesion in a closed chest laboratory animal. Under fluoroscopic control a small plastic truncated cone (5 mm long, outside diameter 3.5 mm tapering to 3.25 mm) with a narrow, central internal lumen (diameter 0.625 mm) was passed over a guide wire into the left anterior descending coronary artery of a closed chest, heparinized pig (n = 6). Regional myocardial blood flow (microsphere technique) distal to the artificial stenosis (distal zone) and in myocardium perfused by the circumflex coronary artery was determined under the following conditions: at rest (control I), at the 10th minute of atrial pacing (190 min^{-1}) and 10 to 15 minutes after discontinuation of pacing (control II). At rest, transmural blood flow distal to the stenosis (1.29 ± 0.32 ml/min per g, mean ± standard deviation) was almost identical to that in the circumflex zone (1.31 ± 0.31, r = 0.93, p <0.01). During atrial pacing transmural flow increased significantly (p <0.01 versus control) in the circumflex zone (1.73 ± 0.27) and then returned to control value (1.34 ± 0.38) after pacing was discontinued. In contrast, transmural flow in the distal zone (1.45 ± 0.40) failed to increase significantly with pacing. In addition, during atrial pacing the endocardial to epicardial blood flow ratio distal to the stenosis decreased from 0.99 ± 0.13 (control I) to 0.68 ± 0.14 (p <0.01), whereas it remained unchanged in the circumflex zone (1.1 ± 0.11 to 1.1 ± 0.08, difference not significant). Finally, the artificial intraluminal stenosis remained patent for the duration of the study (5.1 ± 0.05 hours) in all animals. Thus the intracoronary plastic stenosis is a promising new method for the production of a critical coronary arterial lesion in closed chest laboratory animals.

Although the effects of coronary arterial occlusion on myocardial blood flow and function have proved relatively easy to model, a critical stenosis with reversible myocardial ischemia has posed a more difficult problem for investigators. Available techniques[1–7] require thoracotomy with consequent alteration of normal pericardial physiology and potential disruption of coronary arterial and myocardial nerve supply. Furthermore, the method of creating such a stenosis commonly involves externally constricting the coronary artery until resting blood flow through the vessel is reduced.[8–10] Because most human beings with chronic ischemic heart disease have normal regional blood flow at rest,[11] this aspect of the method may be undesirable.

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Accordingly, we developed a new technique for studying the effects of a severe coronary arterial stenosis on regional myocardial blood flow and left ventricular function. The technique consists of inserting an occlusive plastic truncated cone with a narrow central internal lumen directly into the animal's coronary artery. This can be accomplished rapidly in a closed chest animal using standard cardiac catheterization techniques. Regional blood flow (microsphere technique) in myocardium distal to the stenosis and in myocardium perfused by the circumflex coronary artery was determined at rest and during and after rapid atrial pacing in order to confirm that a critical stenosis had been produced by the device.

Methods

Description of the artificial stenosis: The artificial stenosis was custom-turned on a machinist's lathe from a stock cylinder (diameter 6.4 mm) of Delrin™ (DuPont), a firm; hard, radiolucent plastic material. The device has the shape of a truncated cone and is 5 mm long with an outer diameter tapering from 3.50 to 3.25 mm (Fig. 1, top). An internal lumen bored through the center of the device with a drill bit 0.625 mm in diameter permitted blood to flow through it. The small internal lumen caused an 82 percent reduction in the diameter of the vessel at the point where the artificial stenosis came to rest. To help prevent clotting, the stenosis was coated inside and out with benzalkonium chloride-heparin complex (North American Science Associates, Toledo, Ohio) before placement in the coronary artery. This was accomplished by simply dipping it in the solution for 10 to 15 seconds and then drying it in an oven at 45°C for 10 minutes. The stenosis was recoated with this solution before each use. The surface of the internal lumen was relatively smooth and free of major deformities, although a few rough spots were observed (Fig. 1, bottom).

Animal preparation: Six closed chest pigs (weight 47 to 60 kg) were studied as described later in order to confirm that the device produced a critical coronary stenosis. A double

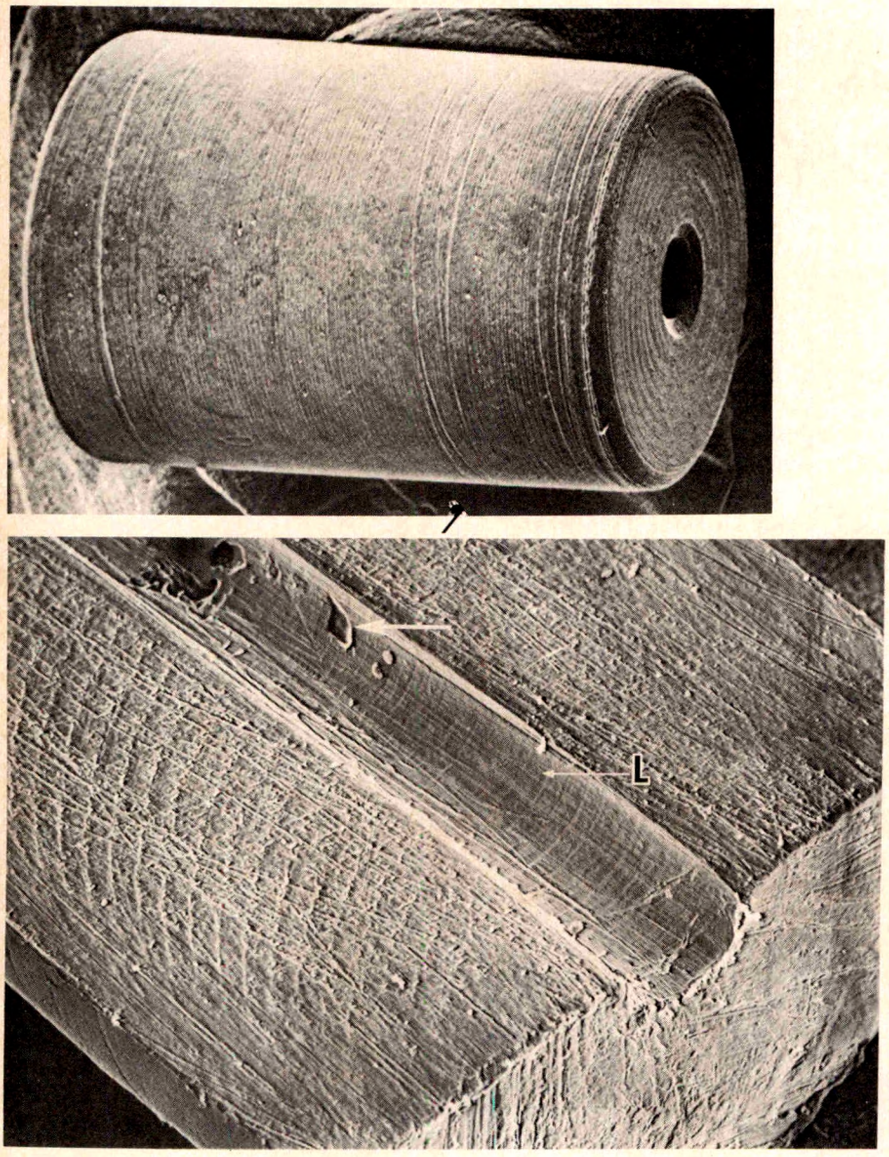

FIGURE 1. Scanning electron micrographs. **Top,** of an artificial stenosis. The external surface is relatively smooth although it is covered with innumerable tiny grooves. The grooves were caused by the machinist's tool as the device was turned on a lathe. The distal surface of the stenosis is visible **at right**. The proximal surface (not shown) appeared similar except for two very small burrs visible at the mouth of the internal lumen. **Bottom,** the surface of the internal lumen (L) of the artificial stenosis. The device has been cut in half along its long axis to permit examination of the lumen. The surface has several small gouges (**arrow**) at its distal end (**upper left**) as well as several ridges extending along its length. Otherwise it is relatively smooth and free of major deformities. (Magnification: **top** ×34, **bottom** ×43, both reduced by 34 percent.)

lumen 8 French catheter was placed in the thoracic aorta through the left femoral artery. The arterial catheter was used to monitor pressure and to obtain samples of blood for determination of pH and partial pressure of oxygen and carbon dioxide. Another cutdown was performed over the right femoral artery and vein. An 8 French angiographic catheter was advanced from the femoral artery under fluoroscopic guide and placed retrograde in the left atrium. The right femoral vein was used to advance another 8 French angiographic catheter into the main pulmonary artery. In addition, a 7 bipolar pacing catheter was placed in the coronary sinus through the right internal jugular vein. Pressure was monitored from all catheters with Statham P23db transducers and recorded on paper with a Hewlett-Packard 8 channel recorder (model 7788A). The left atrial catheter was used for injection of radiolabeled microspheres to determine regional myocardial blood flow.[12] The pulmonary arterial catheter was used for injection of indocyanine green to determine cardiac output by the dye-dilution technique (Cardiac Output Computer, model COCS, Lexington Instruments, Lexington, Massachusetts). After placement of the catheters the animal was systemically anticoagulated with heparin (225 IU/kg intravenously). Thereafter, half of the loading dose was given every hour for the remainder of the study.

An Amplatz catheter was inserted in the right carotid artery and advanced under fluoroscopic control to the origin of the left anterior descending coronary artery (Fig. 2). The artery was visualized by injection of 3 to 5 cc of Renografin,™ and its mid and distal points were marked on the video monitor. After that a Teflon®-coated guide wire with a diameter of 0.533 mm and a 3 cm floppy distal end (Cook Inc., Bloomington, Indiana) was advanced through the Amplatz catheter into the distal portion of the coronary artery. The Amplatz catheter then was removed, leaving only the guide wire within the artery. Next, the proximal end of the wire was inserted through the central lumen of the plastic stenosis. The device was then pushed along the wire and into the coronary artery by means of a 50 cm long, thin-walled flexible plastic catheter (inside diameter 0.76 mm, outside diameter 0.77 mm). Both the wire and "pushing" catheter were then quickly removed, leaving the artificial stenosis firmly in place within the lumen of the coronary artery (Fig. 3).

Experimental protocol: After the stenosis had been placed in the animal's coronary artery, cineangiography was performed with the animal in a 45° left anterior oblique position. This was done to document the location of the stenosis and to be sure that blood continued to flow through it. The angiogram was obtained with Kodak CFX 35 mm film after hand injection of 4 to 6 cc of Renografin. The film was exposed at 60 frames/s at a setting of 80 kV and 150 mA. A Philips 6 inch (152.4 mm) image intensifier with cesium iodide phosphor was

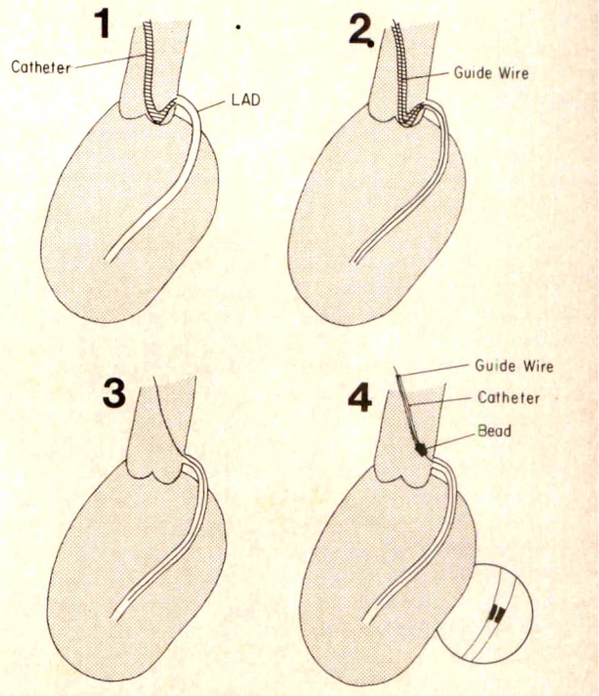

FIGURE 2. Diagram of the procedure for placement of the intracoronary plastic stenosis. Under fluoroscopic control an Amplatz catheter is placed at the origin of the left anterior descending (LAD) coronary artery (**1**). A guide wire (diameter 0.533 mm) is passed through the catheter into the artery (**2**), after which the catheter is removed, leaving the wire in place (**3**). The plastic stenosis is threaded over the wire and advanced into the coronary artery with the aid of a thin, flexible pushing catheter (**4**). The guide wire and pushing catheter are then removed, leaving the stenosis in place (**inset**).

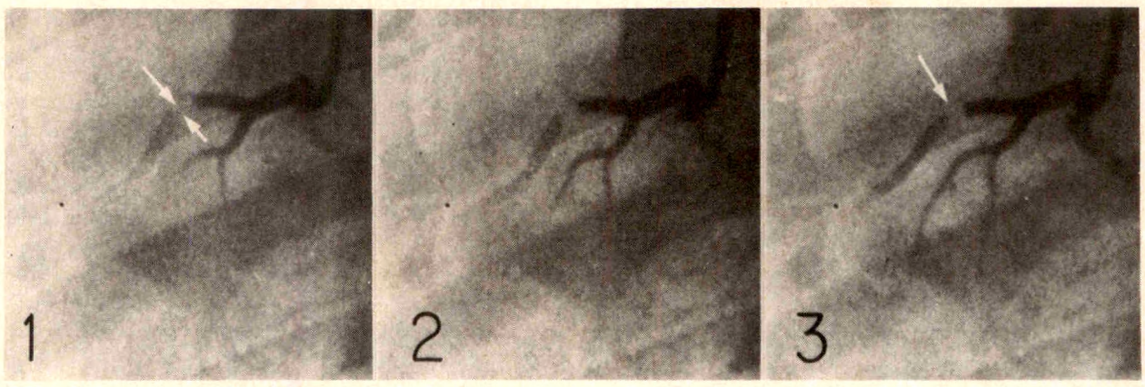

FIGURE 3. Selected sequential frames from a contrast cineangiogram of the left anterior descending coronary artery of one of the animals (0331) used in the study. In **frame 1** the contrast material appears to taper toward the center of the vessel (**area between the two arrows**). In **frame 2** a small centrally placed nub is apparent on the proximal end of the column of dye. In **frame 3** the column of contrast medium proximal as well as distal to the stenosis (radiolucent zone indicated by **arrow**) is squared off. The sequence of images suggests that contrast medium first passes through the central lumen of the stenosis and that blood does not flow around its sides. Note that the distal artery appears to fill at roughly the same rate as the diagonal branches proximal to the stenosis. The resolution of the angiographic system used in this study was 1.5 to 2.0 line pairs/mm.

used. The roentgenographic system employs a fine line grid containing 60 lines with 6 to 1 ratio. It has a 0.6 mm focal spot with tube to film a distance of 28 inches (711.2 mm). Resolution of the system is 1.5 to 2.0 line pairs/mm.

After halothane (0.5 to 1.5 percent) anesthesia was discontinued, all cutdown sites were closed and all catheters secured in place. Next, the animal was moved to a special cage and allowed to awaken from the anesthesia. The animal remained intubated and spontaneously breathed a mixture of 50 percent oxygen and 50 percent nitrous oxide throughout the remainder of the study. The endotracheal tube was suctioned and the animal sighed with a bag inflation device at regular intervals to maintain arterial pH, and partial pressures of carbon dioxide and oxygen within the physiologic range. Heart rate was monitored continuously from the electrocardiogram (lead V_1); arterial, left atrial and pulmonary arterial pressures were also monitored continuously. Sodium thiamylal was given in small doses (20 to 40 mg intravenously) as needed (usually every 60 to 90 minutes) to ensure that the animal rested quietly in its cage. Although sedated, the animal was responsive and had brisk corneal reflexes.

Regional myocardial blood flow was determined by injecting 4 million radiolabeled microspheres (diameter 15 μ) (New England Nuclear, Billerica, Massachusetts) into the left atrium. At the same time a 2 minute reference collection of arterial blood was obtained by means of a Harvard pump. The microspheres were suspended in a solution of 10 percent dextran and 0.01 percent Tween 80™ and sonically dispersed for 15 minutes before injection. A different radioisotope (chosen at random) was used for each injection. Total radioactivity for each injection ranged from 85 to 105 μCi.

After control measurements of hemodynamics and regional myocardial blood flow were made, the animal's heart rate was increased for 10 minutes by atrial pacing at 185 to 190 beats/min. A second set of microspheres was given and pacing discontinued after completion of the reference collection of arterial blood. Ten to 15 minutes later, after heart rate and arterial pressure had stabilized at control levels, a third set of microspheres was given. Cardiac output (green dye technique) was determined just before each injection of microspheres.

In one of the six animals regional myocardial blood flow also was determined during intravenous infusion of adenosine (0.59 mg/kg per min × 10 min). The vasodilator infusion was begun after completion of the second control determination of regional myocardial blood flow. Microspheres were injected at the end of the drug infusion period.

After the completion of flow studies, the animal was removed from its cage and placed on the angiography table. Next, the left anterior descending coronary artery was selectively catheterized, after which a repeat cineangiogram was recorded with identical roentgenographic technique and positioning comparable to that of the initial film. The animal was then killed by injection of potassium chloride directly into the heart.

Postmortem examination: The heart was removed and the location of the stenosis marked with a silk suture. It was then thoroughly washed in tap water and blotted dry. Next the left anterior descending coronary was opened by inserting a Metzenbaum scissor into its orifice and cutting it open along its entire length. The artificial stenosis was removed and inspected for evidence of fibrin deposition or blood clot within its lumen. The surface of the artery was inspected for evidence of dissection or intimal damage.

The heart was then divided into two zones, one encompassing the posterobasal region in an area perfused by the circumflex coronary artery and another along the anterior wall of the left ventricle in a region perfused by that part of the left anterior descending artery which was distal to the stenosis (distal zone). This area was defined visually by following the epicardial distribution of its diagonal branches. Each region in turn was subdivided into cubes weighing approximately 1 g. Each cube was further divided into endocardial and epicardial halves. The samples were placed in preweighed tubes, and the tube and contents reweighed. The radioactivity in each was determined by counting the samples in a gamma well counter (Packard Instruments, Downers Grove, Illinois). A computer was used to correct for spillover of counts from one isotope into the window of another and to calculate regional blood flow in the samples.

Statistical methods: All data are expressed as mean ±1 standard deviation. The null hypothesis that two or more treatment means (such as regional myocardial blood flow in a given zone during and after atrial pacing) did not differ significantly ($p < 0.05$) from that of the control mean (such as regional myocardial blood flow given zone before pacing) was tested by means of a blocked one way analysis of variance and Dunnett's test.[13] The value F for the treatment effect (F[t]) and associated value of p are given for all tests involving regional myocardial blood flow in which the p value is 0.05 or greater.

Results

Technical aspects: Placement of the artificial stenosis was successful in all six cases. Each stenosis lodged within the proximal one third of the left anterior descending coronary artery. The device remained patent for the duration of the study (5.1 ± 0.5 hours) in all six animals. Cineangiograms obtained at the start and finish of each case revealed slight (2 mm) distal migration of the stenosis in only one instance. In all other cases the device did not move from its original location. No angiographic or electrocardiographic evidence of coronary arterial spasm was observed in any animal. Inspection of cine films revealed no evidence of contrast medium passing around the sides of the lesion in any study (Fig. 3). Further, in five of six animals cineangiograms as well as postmortem examination of the heart revealed no evidence of occlusion of any branch of the left anterior descending coronary artery. In the remaining animal a small septal branch was occluded by the stenosis. This was readily apparent when the stenosis was removed because (1) the device was recovered from a position directly over the orifice of the branch, and (2) there was a clearly defined peninsula of pale yellow-tan tissue surrounding the vessel in question. Microsphere activity (all three isotopes) in this specimen was negligible. Finally, there was prompt anterograde filling of the left anterior descending coronary artery beyond the stenosis in all animals (Fig. 3), a finding that suggests that simultaneous retrograde filling of the vessel was unlikely.

There was no gross evidence of damage to the intimal lining of the left anterior descending coronary artery in any animal. Likewise there was no gross evidence of platelet or fibrin deposition within the lumen of the bead.

Regional myocardial blood flow (Table I, Fig. 4): Regional myocardial blood flow distal to the stenosis was compared with that in the circumflex arterial zone

TABLE I

Regional Blood Flow (ml/min per g) in Myocardium Distal to an Artificial Stenosis of the Left Anterior Descending Artery (distal zone) and in Myocardium Perfused by a Normal Coronary Artery (circumflex zone)

	Control I	Atrial Pacing	Control II
Distal zone			
Transmural	1.28 ± 0.34	1.45 ± 0.40	1.28 ± 0.42
Endocardium	1.26 ± 0.34	1.16 ± 0.37	1.20 ± 0.41
Epicardium	1.28 ± 0.37	1.72 ± 0.48*	1.35 ± 0.47
Endo/epi ratio	0.99 ± 0.13	0.68 ± 0.14*	0.91 ± 0.17
Circumflex zone			
Transmural	1.31 ± 0.31	1.73 ± 0.27*	1.34 ± 0.38
Endocardium	1.37 ± 0.11	1.82 ± 0.33*	1.42 ± 0.40
Epicardium	1.26 ± 0.36	1.65 ± 0.24*	1.26 ± 0.37
Endo/epi ratio	1.10 ± 0.11	1.10 ± 0.08	1.14 ± 0.07
Distal to circumflex zone flow ratio			
Transmural	0.97 ± 0.10	0.82 ± 0.11*	0.95 ± 0.10
Endocardial	0.92 ± 0.13	0.63 ± 0.14*	0.84 ± 0.15
Epicardial	1.01 ± 0.11	1.02 ± 0.15	1.06 ± 0.11

* $p < 0.01$ versus control I.
Endo = endocardium; Epi = epicardium.

for each phase of the study. At rest the ratio of transmural flow for the two zones was 0.97 ± 0.10. Compared with the control level (1.28 ± 0.32 ml/min per g), transmural flow in myocardium distal to the stenosis did not change significantly during (1.45 ± 0.40) or after (1.28 ± 0.42) atrial pacing ($F[t] = 1.799$, $p = 0.22$). In contrast, flow in the circumflex arterial zone increased with pacing from a control value of 1.31 ± 0.31 to 1.73 ± 0.27 during pacing ($p < 0.01$) and then returned to a level similar to the initial control level (1.34 ± 0.38) after discontinuation of pacing. As a result, the transmural flow ratio (distal to circumflex) decreased to 0.82 ± 0.11 ($p < 0.01$) during pacing but returned to the initial control level (0.95 ± 0.10) 10 minutes after pacing was stopped.

Endocardial blood flow distal to the stenosis decreased from a control value of 1.26 ± 0.34 to 1.16 ± 0.37 during atrial pacing and returned to a level similar to the control value (1.20 ± 0.41) 10 minutes after pacing was terminated ($F[t] = 0.544$, $p = 0.60$). In contrast, endocardial flow in the circumflex zone increased from a control level of 1.37 ± 0.11 to 1.82 ± 0.33 during atrial pacing ($p < 0.01$) and returned to control levels (1.42 ± 0.40) when pacing was terminated. The endocardial blood flow ratio (distal to circumflex) decreased from 0.92 ± 0.13 to 0.63 ± 0.14 ($p < 0.01$) during pacing and returned toward control after pacing was discontinued (0.84 ± 0.15).

Epicardial blood flow during atrial pacing increased significantly ($p < 0.01$) and to a comparable extent in epicardium distal to the stenosis (1.72 ± 0.48 versus control 1.28 ± 0.37) and in the circumflex zone (1.65 ± 0.24 versus control 1.26 ± 0.36). Epicardial flow returned to control levels (1.35 ± 0.47 and 1.26 ± 0.37, respectively) after pacing was discontinued. The epicardial blood flow ratio (distal to circumflex) did not change significantly compared with the control value (1.01 ± 0.11) during (1.02 ± 0.15) or after (1.06 ± 0.11) atrial pacing ($F[t] = 0.835$, $p = 0.46$).

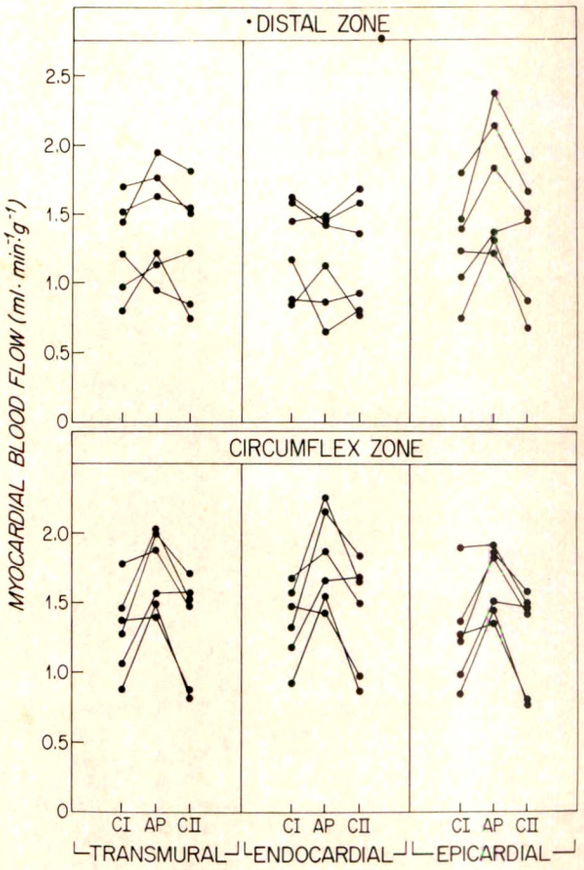

FIGURE 4. Regional myocardial blood flow (ml/min per g) for each phase of the study is shown for transmural, endocardial and epicardial samples distal to the left anterior descending arterial stenosis (**top**) and in the circumflex arterial region (**bottom**). Each point represents one animal. Note that compared with control I (CI), transmural flow during atrial pacing (AP) increased significantly in the circumflex zone but not in the distal zone. Endocardial flow increased significantly during atrial pacing only in the circumflex area. Flow was augmented in epicardial samples during atrial pacing to a comparable extent in both the distal and circumflex regions. After cessation of atrial pacing (CII), flow in all samples returned to levels that did not significantly differ from that of control I.

Finally, the endocardial to epicardial blood flow ratio in the distal zone decreased from 0.99 ± 0.13 to 0.68 ± 0.14 during atrial pacing ($p < 0.01$) and then returned to control (0.91 ± 0.17) after pacing was stopped. In contrast, the endocardial to epicardial flow ratio in the circumflex region did not change significantly from the control value (1.1 ± 0.11) during (1.1 ± 0.08) or after (1.14 ± 0.07) atrial pacing ($F[t] = 1.085$, $p = 0.37$).

Infusion of adenosine in one animal resulted in marked disparity between transmural flow in the circumflex and distal left anterior descending zones (Fig. 5). Thus transmural flow more than tripled (1.49 to 4.91) in the circumflex zone, whereas it increased by only 11 percent (1.51 to 1.69) in the zone distal to the stenosis. Further, endocardial blood flow distal to the stenosis remained essentially fixed, whereas in the circumflex zone it increased considerably in response to adenosine and to a lesser extent in response to atrial pacing. Epicardial blood flow distal to the stenosis increased

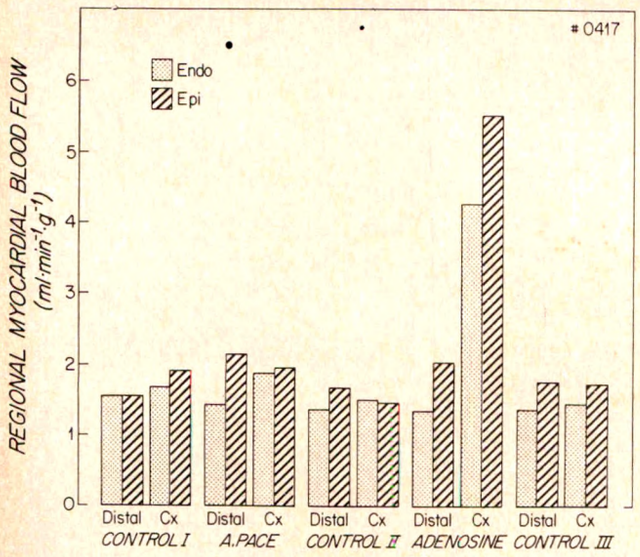

FIGURE 5. Regional myocardial blood flow (ml/min per g) in one animal (0417) that was given adenosine to test the vasodilatory reserve of the distal left anterior descending (Distal) and circumflex (Cx) coronary arterial beds. Note that compared with control period I, endocardial blood flow distal to the stenosis remained unchanged after atrial pacing (A. Pace) and adenosine infusion. In contrast, endocardial flow in the circumflex region increased moderately in response to pacing and markedly in response to adenosine infusion. Blood flow in epicardium distal to the stenosis increased to an extent comparable with that in the circumflex region during atrial pacing. However, during infusion of adenosine, epicardial flow in the circumflex zone greatly exceeded that in the distal zone. Note also that epicardial flow in the distal zone was essentially the same during both interventions.

modestly and to a comparable extent in response to both pacing and adenosine infusion.

Hemodynamics: Hemodynamic observations associated with each phase of the study were as follows. In response to atrial pacing the rate-pressure product (mm Hg/min $\times 10^2$) increased from 140 ± 47 to 262 ± 24 ($p < 0.001$) and then decreased to 137 ± 35 after cessation of pacing. Mean left atrial pressure during atrial pacing (13.7 ± 4.9 mm Hg) was significantly higher ($p < 0.01$) than either before (5.5 ± 2.6) or after (5.0 ± 3.2) pacing. Diastolic arterial pressure did not change significantly during the study (114 ± 9 mm Hg before pacing, 115 ± 11 with pacing and 118 ± 8 after pacing). Cardiac output decreased modestly but significantly ($p < 0.05$) during (4.4 ± 0.8 liters/min) and after pacing (4.4 ± 1.0 liters/min) compared with prepacing the level (4.9 ± 0.9 liters/min).

Discussion

Demonstration of experimentally produced critical coronary stenosis: The present study demonstrates that a critical intraluminal coronary arterial stenosis can be created and maintained for over 5 hours in a closed chest animal. The data obtained from the pacing part of the study confirm that a critical stenosis was produced by the device. Thus, although transmural blood flow distal to the left anterior descending arterial stenosis was similar at rest to that in the circumflex arterial zone, it failed to increase significantly in the distal area during atrial pacing. Further, both the transmural and endocardial distal to circumflex flow ratios decreased significantly during atrial pacing and then returned to control levels after pacing was discontinued. In addition, during pacing the endocardial to epicardial flow ratio decreased considerably in myocardium distal to the stenosis but remained unchanged in the circumflex zone. Thus our data indicate that the subendocardial layer of the heart is most vulnerable to ischemia, an observation consistent with the results of previous studies by other investigators.[14–17] In addition, our data indicate that some vasodilator reserve persists in epicardial vessels distal to a critical coronary stenosis. This finding is in accord with the results of a recent study by Gallagher et al.[17] Finally, it should be noted that others[18,19] have observed that resting blood flow may be decreased distal to an extraluminal artificial stenosis that is 5 mm long and that decreases luminal diameter by only 60 percent. The reason for this difference from our results is uncertain, but it may well be related to differences in the way in which the stenosis was created (that is, intraluminal versus extraluminal placement) as well as other differences in method (for example, open versus closed chest animals, general anesthesia versus mild sedation, and species differences between the dog and the pig). Whatever the reason for this difference, our data, nevertheless, show that the intraluminal stenosis impairs flow when the animal is stressed and that such changes are reversible when the stress is removed. Taken together our findings support the contention that a critical stenosis was produced by the device.

Advantages of the method: In addition to the speed and ease with which the artificial stenosis can be created, this technique offers other advantages. First, open chest surgery with its attendant trauma and alterations in the normal physiologic characteristics of the pericardium is avoided. In addition, possible disruption of normal myocardial and coronary arterial nerve supply is also avoided. Second, the ability to place a critical lesion of known dimensions within the lumen of the coronary artery allows one to assess its effects on regional function and blood flow during a stress intervention without introducing experimental errors that could be caused by decreasing flow under resting conditions. Third, because the artificial stenosis causes a rigid lesion with a constant exit angle and a fixed diameter, its effects on regional myocardial blood flow can be assessed in the absence of factors (such as spasm or collapse of the vessel at the site of the lesion) that could change the geometric characteristics of the lesion and thereby alter its severity.[20–23] The fixed proximal nature of the stenosis also should be helpful for studying the effects of a change in peripheral coronary arteriolar resistance on regional myocardial blood flow. Fourth, by placing an artificial stenosis in any or all of the other coronary arteries one could model multivessel coronary disease.

Limitations of the method: Despite its advantages this technique has limitations that may reduce its utility in some circumstances. It is possible for the device to

occlude a side branch of the artery into which it is inserted and thus produce a small zone of ischemia or infarction. Depending on the nature of the study, this occurrence (which is easily recognized) may or may not require that the animal be eliminated from the data analysis. Although the precise location within a given coronary artery cannot be controlled, the dimensions of the stenosis will dictate whether it comes to rest in the proximal, mid or distal portion of the vessel. The highly flexible nature of the guide wire and pushing catheter make it impossible to advance a device 3.5 mm in diameter into a more distal portion of a vessel with a substantially smaller diameter. Nevertheless, if for some reason the artificial stenosis had to be precisely positioned at a very specific portion of the vessel, problems could arise because of an inability to control the exact location where the stenosis comes to rest. In addition, once the device has been inserted it is not possible to adjust its position or remove it.

Adaptation of method to acute and long-term physiologic studies: One reason this method was developed was to avoid technical and physiologic problems associated with coronary arterial surgery in the preparation of animals for physiologic studies. In this regard, the microsphere technique was chosen to measure regional myocardial blood flow because it is very easy to catheterize the left atrium and thereby administer microspheres without having to operate on the animal. The microsphere technique itself has been extensively validated by Domenech et al.[12] and Heymann et al.[24] At present it is the most reliable and readily available way to assess the transmural distribution of regional myocardial blood flow in the same animal under a variety of conditions. However, if one wished to study coronary flow velocity with a flow probe or regional myocardial function with ultrasonic crystals, there is no reason why the artificial stenosis could not be inserted first and the required surgery and instrumentation performed immediately thereafter. The animal could then be used for acute open chest studies. Even under these conditions the intraluminal fixed nature of the lesion would offer an advantage over conventional methods of creating a critical coronary stenosis. Furthermore, although it might be difficult to maintain systemic anticoagulation for 1 or 2 weeks in order to permit the animal to recover from surgery, it would be possible. Accordingly, it should be possible to adapt this technique for use in chronically instrumented animals.

In summary, we have developed a simple and effective method for creating a critical intraluminal coronary arterial stenosis in a closed chest laboratory animal. This method makes it possible to avoid many of the problems associated with open chest surgery and general anesthesia in the preparation of animals for studies requiring a critical coronary arterial lesion. The technique does have certain limitations. Nevertheless, the ability to create and maintain a fixed, critical, intraluminal coronary arterial stenosis in a closed chest animal provides an improved model for the study of myocardial blood flow and left ventricular function.

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Differential Effects of Renografin-76 on the Ischemic and Nonischemic Myocardium

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The effects of intracoronary diatrizoate meglumine and diatrizoate sodium (Renografin-76) on regional contraction were examined in the normal coronary circulation and during partial (50 percent) coronary occlusion in 11 dogs using strain and length gauges. Intracoronary injections of Renografin-76 (1.5 cc) (1,690 mosM/liter; 0.19 mEq Na/ml), equiosmolar dextrose solution and 0.19 mEq Na^+/ml saline solution were made randomly. Renografin-76 caused a decrease in preejection tension to 87.4 ± 4.3 percent ($p < 0.025$), total tension to 74.6 ± 3.3 percent ($p < 0.01$) and ejection tension to 11.9 ± 12.6 percent ($p < 0.001$) of control value. Segment length increased to 106.7 ± 7.3 percent of control value. These changes lasted only 12 ± 2 (range 5 to 20) seconds (mean ± standard error of the mean). During partial coronary occlusion and after injection of Renografin-76, preejection tension decreased from 91.7 ± 6.3 to 53.8 ± 3.9 percent ($p < 0.01$), total tension from 89.9 ± 5.0 to 59.7 ± 3.5 percent ($p < 0.01$) and ejection tension from 22.8 ± 8.1 to 17.8 ± 10.9 percent, whereas segment length increased from 112.7 ± 3.7 to 130.7 ± 4.6 percent ($p < 0.01$) of control value. In contrast to findings in the normal coronary circulation, tension and length changes lasted 54 ± 16 (range 15 to 180) seconds ($p < 0.05$). The hyperemic response during normal coronary circulation was completely abolished during partial coronary occlusion. Prior administration of nitroglycerin did not shorten the duration of the myocardial depressant effects of Renografin. Injections of equiosmolar dextrose or saline solution produced qualitatively similar but quantitatively less marked changes. Thus, intracoronary Renografin-76 has an accentuated and prolonged depressant effect on the ischemic as compared with the normally perfused myocardium; this effect is not solely due to its hyperosmolarity or sodium concentration.

Selective coronary arteriography is being widely used in the evaluation of patients with coronary artery disease. Although the morbidity and mortality associated with this technique have declined considerably with increasing experience, the attendant risks are higher in patients with acute ischemia[1,2] than in other groups. These risks may partly be related to the myocardial depressant effects of the contrast medium being used.[3–5] Although several experimental and clinical studies have evaluated the effects of the intracoronary injections of contrast material on global left ventricular performance, there is paucity of information on the regional contractile performance of the ischemic and nonischemic left ventricular zones during selective coronary injections.

The present experimental study was therefore designed to evaluate the differential effects of the intracoronary injections of a commonly used contrast medium (Renografin-76®) on the contractile function of nonischemic and ischemic myocardium after partial coronary occlusion.

Methods

Experiments were performed in 17 mongrel dogs, weighing 25 to 30 kg, anesthetized with sodium pentobarbital (30 mg/kg body weight, intravenously), intubated and ventilated with room air using a Harvard respirator. Electrocar-

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diographic lead I or II, or both, was recorded continuously in each experiment. Aortic pressure was monitored with use of a stiff catheter positioned in the ascending aorta. A 3F radiopaque catheter was positioned in either the left anterior descending or the circumflex coronary artery using the method described previously.[6] A left anterolateral thoracotomy was performed and the heart was supported in a pericardial cradle. A 2 to 3 cm long segment of the coronary artery was exposed and mobilized. A specially designed adjustable screw clamp was passed around the coronary artery proximal to the tip of the intracoronary catheter for producing graded reduction in coronary blood flow.[7] An electromagnetic flow probe (Micron MV 1001-B) was sequentially placed distal to the tip of the catheter to monitor coronary flow distal to the occlusion.

Two Walton-Brodie strain gauge arches were placed with deep sutures at a 30 to 40 percent stretch, one in the area subserved by the vessel containing the intracoronary catheter (potentially ischemic zone) and the other in the remote unaffected area (nonischemic zone). A previously calibrated mercury-in-Silastic® segment length gauge was also sutured adjacent and parallel to the strain gauge arch in each zone.[6–8]

Partial coronary occlusion was produced by tightening the adjustable microscrew clamp around the coronary artery and monitoring distal coronary flow until a stable 50 percent (45.3 ± 3.6) reduction in coronary flow was achieved. At least 15 minutes was allowed for the contractile function to stabilize after partial coronary occlusion.

Intracoronary test solutions: The following solutions (1.5 cc each) were injected into the coronary artery through the radiopaque catheter in random order before and at least 15 minutes after partial coronary occlusion and their effect elucidated on the contractile function and coronary blood flow to the partially ischemic and nonischemic myocardium: (1) Renografin-76® (diatrizoate meglumine and diatrizoate sodium); (2) glucose solution containing 1,690 milliosmoles/liter; and (3) saline solution (0.19 mEq Na^+/ml). The osmolarity of the latter two solutions was similar to that of Renografin-76. Renografin (1.5 cc) was sufficient for adequate visualization of the coronary artery on fluoroscopy. All three solutions were injected at a temperature of 37° C and the duration for each injection was kept constant at 2 to 3 seconds. At least 10 minutes was allowed between injections for the effect of the previous injectate to dissipate and all measurements of contractile parameters to return to baseline.

In six experiments, 300 to 400 μg bolus dose of intravenous nitroglycerin was injected before the injection of Renografin-76 to test whether the myocardial depressant effects of intracoronary Renografin could be prevented by prior administration of nitroglycerin.

Measurements: As an index of contractile performance of the myocardium, the following variables were measured and expressed as percent of control value before and after each injection: (1) total tension, (2) preejection tension, (3) ejection tension, and (4) phasic segment length. Continuous recordings of segment tension and length were made on an Electronics for Medicine oscilloscopic recorder at paper speeds of 50 to 100 mm/s. The duration of depressant effects of each intervention was interpreted as the time from the completion of the injection to the return of contractile variables to baseline. Statistical analysis was performed by Student's *t* test for paired values.

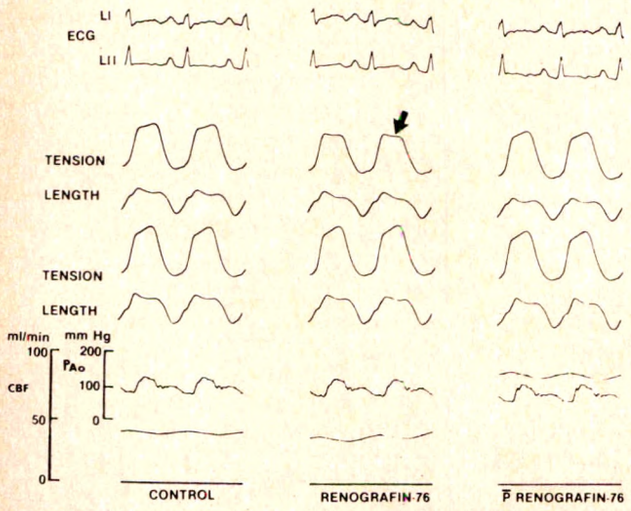

FIGURE 1. Effect of intracoronary injection of Renografin-76 on segment tension, length and coronary blood flow of the nonischemic zone. Recordings (**from top to bottom**) include electrocardiographic (ECG) leads I and II, tension and length from the potentially ischemic zone before coronary occlusion, tension and length from the nonischemic remote zone, aortic pressure (P_{Ao}) and coronary blood flow (CBF). The injection of Renografin-76 causes a rapid diminution in the ejection phase of tension development, marked by a negative slope (**arrow**) in addition to a decrease in preejection and total tension. There was no significant change in segment length. The changes in segment tension were immediately reversible. There was a marked increase in coronary blood flow immediately after the injection indicating a hyperemic response.

Results

Effect of Renografin-76 on normally perfused myocardium: Figure 1 demonstrates the characteristic pattern of tension and segment length changes before and after intracoronary injection of Renografin-76. Immediately after the completion of the injection, there was a rapid and progressive diminution of tension development in the ejection phase marked by a negative slope. In addition, the preejection and total tensions were reduced significantly. Segment length did not show a significant change. The changes in tension and length returned to control levels within 5 to 20 seconds (mean ± standard error of the mean 12 ± 2) after injection of Renografin-76 (Fig. 2).

The quantitative changes in tension and length variables are demonstrated in Figure 3. The intracoronary injection of Renografin-76 caused significant decreases in preejection tension to 87.4 ± 4.3 percent ($p < 0.025$), total tension to 74.6 ± 3.3 percent ($p < 0.01$) and ejection tension to 11.9 ± 12.6 percent ($p < 0.001$) of control values. Phasic segment length increased insignificantly to 106.7 ± 3.7 percent of control value.

Coronary flow showed a marked hyperemic response after the injection of Renografin-76 (Fig. 1). There was a transient 1.8 to 3.8-fold (mean 2.5 ± 0.2) increase in coronary blood flow (from 38.2 ± 3.7 to 95.4 ± 6.9 ml/min) that reached a peak 7 to 12 seconds after the injection and slowly returned to control value over 2 minutes.

Effect of Renografin-76 on ischemic myocardium (Fig. 4 to 6): Partial coronary occlusion (45.3 ± 3.6 percent reduction in coronary blood flow) caused significant reduction in preejection tension to 91.7 ± 6.3 percent ($p < 0.05$), total tension to 89.9 ± 5.0 percent (p

<0.01) (Fig. 4) and ejection tension to 22.8 ± 8.1 percent (p <0.001) of control values. Segment length increased to 112.7 ± 3.7 percent (p <0.025) of control value. After injection of Renografin-76, the preejection tension decreased from 91.7 ± 6.3 to 53.8 ± 3.9 percent (p <0.01) and total tension decreased similarly from 89.9 ± 5.0 to 59.7 ± 3.5 percent of control value (p <0.01) (Fig. 4). Ejection tension was reduced from 22.8 ± 8.1 to 17.8 ± 10.9 percent of control value. Phasic segment length, which had increased to 112.7 ± 3.7 percent after partial coronary occlusion increased further to 130.7 ± 4.6 percent of control value (p <0.01) (Fig. 4). In contrast to findings in the nonischemic myocardium, the changes in tension and length were prolonged and returned to control value (post-coronary occlusion level) in 15 to 180 (mean 54 ± 16) seconds (p <0.05) after injection of Renografin-76 (Fig. 5).

The coronary flow through the partially occluded vessel actually decreased from 20.6 ± 2.5 to 14.8 ± 2.6 ml/min after injection of Renografin-76, returning to preinjection levels in 10 to 110 seconds. Hyperemic response was completely abolished (Fig. 6).

Comparative effects of Renografin-76, hypertonic dextrose and hypertonic saline solutions (Figs. 7 and 8): After intracoronary injections of hypertonic dextrose or hypertonic saline solution, the changes in preejection tension, ejection tension, total tension and segment length were qualitatively similar but quantitatively less marked than those produced by Renografin-76 in both normally perfused and ischemic myocardium. The peak hyperemic coronary flow after injection of hypertonic saline or dextrose solution correlated well with that produced by Renografin-76 (r = 0.92) in the normally perfused myocardium. However, the hyperemic response was abolished after partial coronary occlusion.

Effect on remote myocardium, heart rate and blood pressure: The tension and length parameters in the remote myocardium unperfused by the vessel injected with Renografin-76 or saline or dextrose solution remained unchanged following injection of each agent. Similarly, the heart rate and blood pressure remained unaffected by the intracoronary injections both when the myocardium was normally perfused and during partial coronary occlusion.

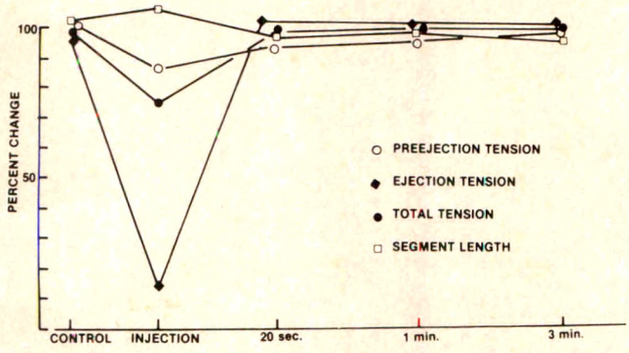

FIGURE 2. Temporal sequence of changes in tension and length variables of the normally perfused (nonischemic) myocardium after the intracoronary injection of Renografin-76.

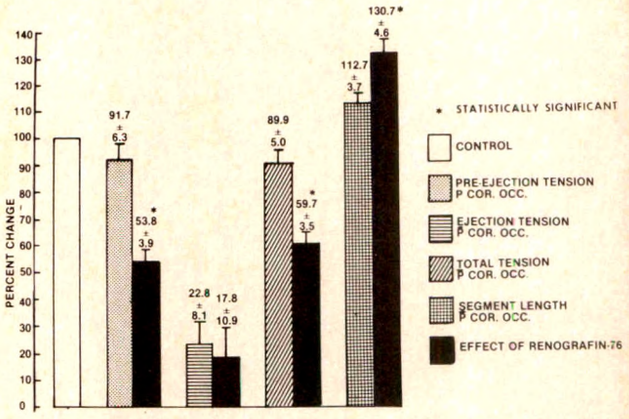

FIGURE 4. Effect of intracoronary injection of Renografin-76 on tension and length variables of the ischemic myocardium (after partial coronary occlusion [P COR. OCC.]). Values are expressed as percent of control value.

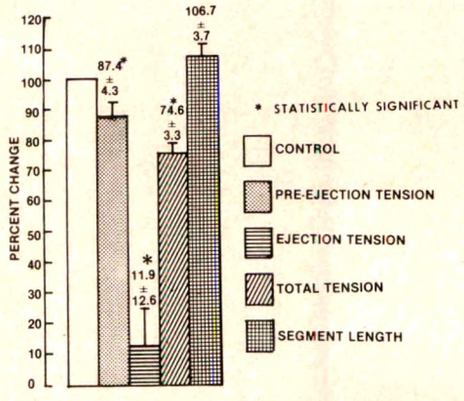

FIGURE 3. Effect of intracoronary injection of Renografin-76 on tension and length variables of the nonischemic myocardium. Values are expressed as percent of control value.

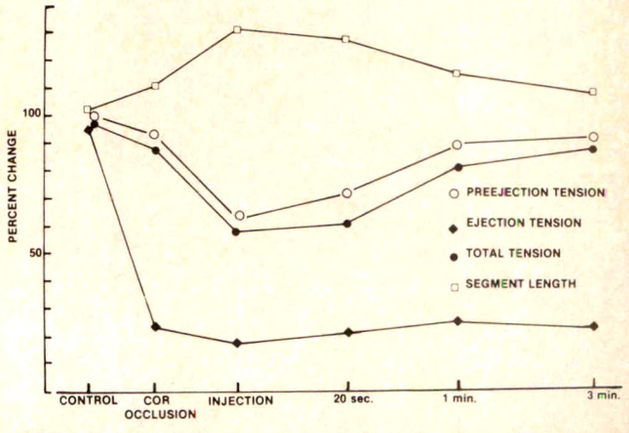

FIGURE 5. Temporal sequence of changes in tension and length variables of the ischemic myocardium (after partial coronary [COR] occlusion) after the intracoronary injection of Renografin-76.

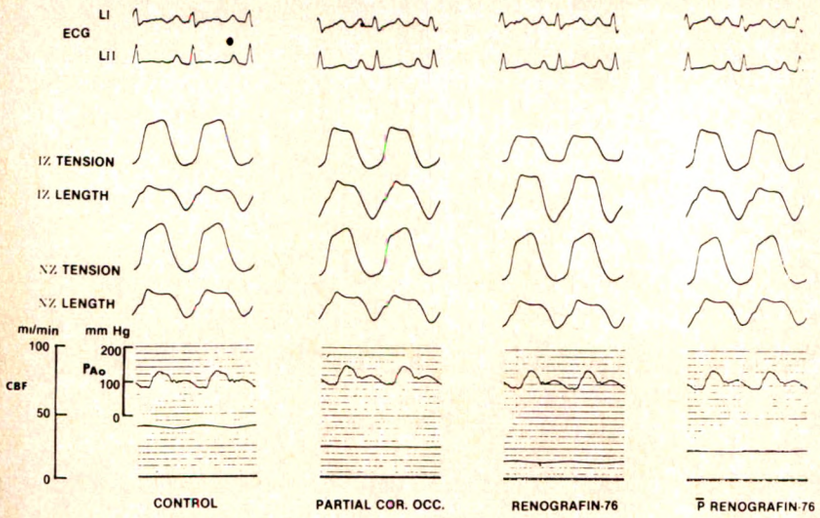

FIGURE 6. Effect of intracoronary injection of Renografin-76 on segment tension, length and coronary blood flow (CBF) of the ischemic myocardium after partial coronary occlusion. Recordings (**from top to bottom**) include electrocardiographic (ECG) leads I and II, tension and length from the ischemic zone (IZ) after partial coronary occlusion (COR. OCC.), tension and length from the nonischemic zone (NZ), aortic pressure (P_{Ao}) and coronary blood flow (CBF). Partial coronary occlusion produced a significant decrease in tension with loss of ejection tension and increase in segment length. After (P) the injection of Renografin-76, there was further decrease in tension and increase in length of the ischemic zone which returned to near post-coronary occlusion levels after 54 ± 16 seconds. Coronary blood flow decreased further after injection of Renografin-76 and did not show a hyperemic response after the injection (compare with Fig. 1).

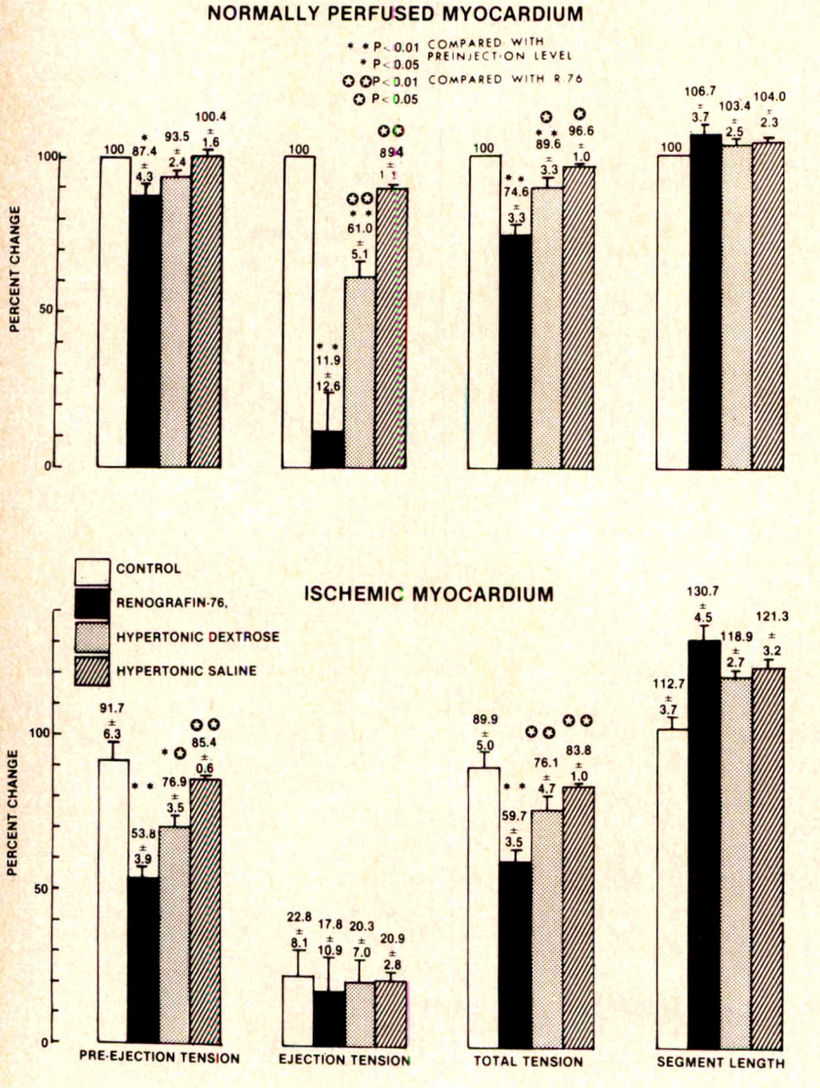

FIGURE 7. Comparative effects of intracoronary injection of Renografin-76 (R-76), and hypertonic dextrose and hypertonic saline solutions on normally perfused and ischemic myocardium. Values are expressed as percent of control value.

Effect of nitroglycerin on the myocardial depressant effects of Renografin-76: Prior administration of intracoronary nitroglycerin did not prevent the myocardial depressant effects of Renografin-76. In the normally perfused myocardium, injection of Renografin-76 caused the total tension to decrease to 71.3 ± 7.5 percent, preejection tension to 79.5 ± 6.9 percent and ejection tension to 35.8 ± 11.7 percent of control value. These variables returned to control value 8 to 30 (mean 15.3 ± 7.0) seconds after injection of Renografin-76.

After partial coronary occlusion and administration of nitroglycerin, the injection of Renografin-76 caused the total tension to decrease from 73.0 ± 9.8 to 60 ± 11.0 percent ($p < 0.01$), preejection tension from 76.0 ± 9.1 to 72.1 ± 8.6 percent ($p < 0.01$) and ejection tension from 50.5 ± 9.5 to −4.7 ± 3.8 percent ($p < 0.01$) of control. These variables returned to control value (post-occlusion level) in 25 to 70 (mean 46.7 ± 21.3) seconds.

Discussion

Considerable interest has been focused on the myocardial depressant effects of the contrast media used for coronary arteriography and ventriculography.[3–5,9–11] However, most studies have compared various contrast media and their ionic concentrations and osmolar aspects to determine the relative safety of each medium.[9–11] These studies have indicated that intracoronary injection of contrast medium results in a decrease in regional contraction as well as in indexes of global left ventricular performance when the coronary perfusion is normal. However, there is little information about the effects of contrast medium on regional performance of the ischemic myocardium. A recent study by Sos and Baltaxe[12] indicates that in patients with coronary disease, there is little difference in the left ventricular ejection fraction as well as regional contractility fraction in the ventriculograms performed before and after coronary arteriography.

Myocardial depressant effects of contrast medium on normal and ischemic myocardium: The present study indicates that when Renografin-76 is injected into a coronary artery, the subserved myocardial zone demonstrates a marked loss in ejection tension and total tension and a slight increase in segment length (Fig. 1) These changes are essentially similar to those produced by the effects of transient coronary occlusion manifesting as an immediate loss of ejection tension, a negative slope in the ejection phase of tension development and a decrease in preejection and total tension.[8] A negative change in ejection tension was not seen when equiosmolar solutions (hypertonic saline and hypertonic glucose) were injected (Fig. 8), thereby indicating that the myocardial depressant effect of Renografin-76 is not dependent on its hyperosmolarity. The contractile changes in the presence of an unobstructed coronary artery were essentially transient and were reversible in less than 20 (mean 12 ± 2) seconds (Fig. 2). In contrast to the effects of an injection made in a normal coronary artery, when partial coronary occlusion (45.3 ± 3.6 percent reduction in coronary blood flow) was produced, the effects of intracoronary injection of Renografin-76 lasted considerably longer (15 to 180 seconds, mean 54 ± 16) (Fig. 5). Renografin-76 produced further augmentation in the decrease in regional preejection tension, ejection tension, total tension and the increase in phasic segment length produced by partial coronary occlusion (Fig. 4). This study thus indicates that the myocardial depressant effects of an intracoronary injection of Renografin-76 in the ischemic zone are more pronounced than in the normally perfused myocardium and are 4–5 times more prolonged. Neither of these effects could be abolished by prior administration of nitroglycerin.

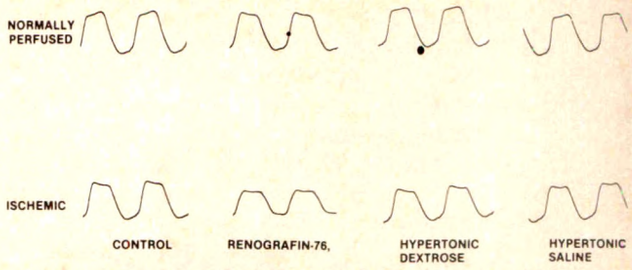

FIGURE 8. Comparative effects of Renografin-76 and hypertonic dextrose and hypertonic saline solution on tension development of the normally perfused and ischemic myocardium. Whereas intracoronary Renografin-76 produced loss of ejection tension (negative slope in ejection phase), ejection tension was maintained during injection of hypertonic dextrose or saline solution. The effects of Renografin-76 were quantitatively more marked than those produced by either of the latter solutions.

Mechanism of negative inotropic effects of contrast medium: The negative inotropic effect of contrast medium has been thought to be related to the medium's hyperosmolarity, high sodium concentration, absence of calcium ions, or the induced transitory ischemia.[13–15] In the present study, neither of the equiosmolar solutions (hypertonic saline or glucose) decreased the indexes of regional contraction to the extent produced by Renografin-76, although glucose had a more depressant effect than did saline (Fig. 7 and 8). In their clinical studies, Cohn and co-workers[16] showed that intraventricular injection of glucose and of Renografin-76 had quantitatively different effects on systemic hemodynamics. These observations suggest that neither hyperosmolarity nor the sodium concentration, in itself, is the sole factor causing myocardial depression.

Role of coronary flow reserve: Previous studies have shown that the intracoronary injection of contrast medium produces a rapid increase in coronary blood flow (hyperemic flow) followed by a gradual decrease to control levels.[14] When coronary flow reserve (that is, autoregulatory reserve) is exhausted, as in situations in which coronary stenosis is severe enough to reduce flow, no increment in flow is observed after the injection of contrast medium.[17–19] Recently, this coronary flow response after injection of contrast medium has been used for assessing coronary flow reserve in man.[20] In the

present study, the diminished myocardial contraction caused by Renografin-76 in the presence of a normal coronary circulation, was restored immediately during hyperemic flow. In contrast, after partial coronary occlusion, the myocardial depressant effects of Renografin-76 on the ischemic myocardium were relatively persistent and associated with a further reduction in coronary flow in contrast to the hyperemic flow observed in the unobstructed coronary artery. Thus, coronary flow reserve appears to play an important role in determining the duration of the depressant effects produced by injection of contrast medium. These findings are consistent with the clinical observations of Gensini et al.,[21] who demonstrated that among various patients, the increase in left ventricular end-diastolic pressure after coronary arteriography was most significant in those with severe coronary artery disease. They assumed that these findings were due to diminished myocardial contraction resulting from ischemic or fibrotic changes, or both.

Prior administration of nitroglycerin did not shorten the duration of the myocardial depressant effects of Renografin-76 on the ischemic myocardium in our study. This finding further supports the observation that, in the presence of a fixed coronary stenosis, coronary flow reserve may be an important determinant of the prolonged duration of the myocardial depressant effects of the contrast medium.

Clinical implications: There is still debate regarding the indications for coronary arteriography in patients with acute ischemic heart disease. Although the incidence of complications of coronary arteriography has decreased since the time when Renografin-76 was adopted as the contrast medium of choice,[22] these patients are still believed to be a high risk group. Because of the increased severity and prolonged duration of myocardial depressant effects of the contrast medium on the ischemic myocardium, sufficient time should be allowed between coronary injections. Although it is difficult to extrapolate experimental observations to clinical situations, our data may be particularly relevant to coronary injections in the presence of left main coronary arterial stenosis. In the presence of a critical left main stenosis sufficient to abolish hyperemic response to the contrast medium, severe and persistent myocardial depressant effects may jeopardize an extensive mass of the left ventricular myocardium and thus produce severe hypotension or left ventricular failure, or both. The risk of coronary arteriography is recognizably high in this group of patients.

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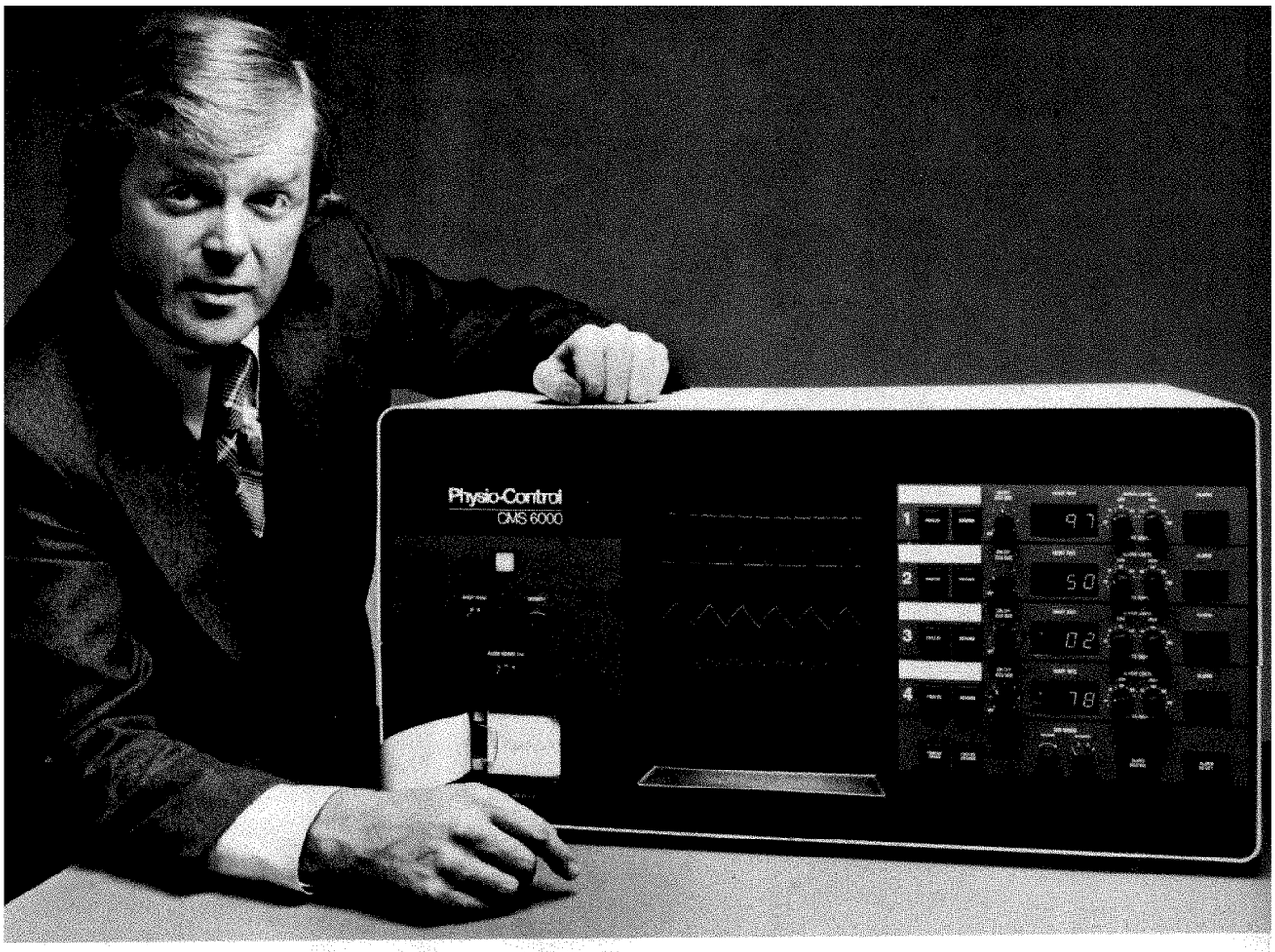

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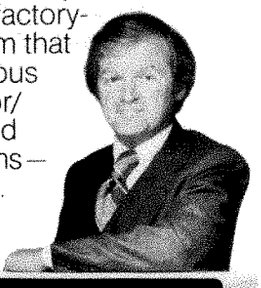

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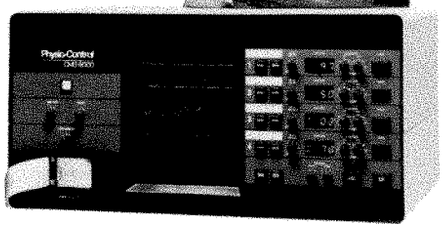

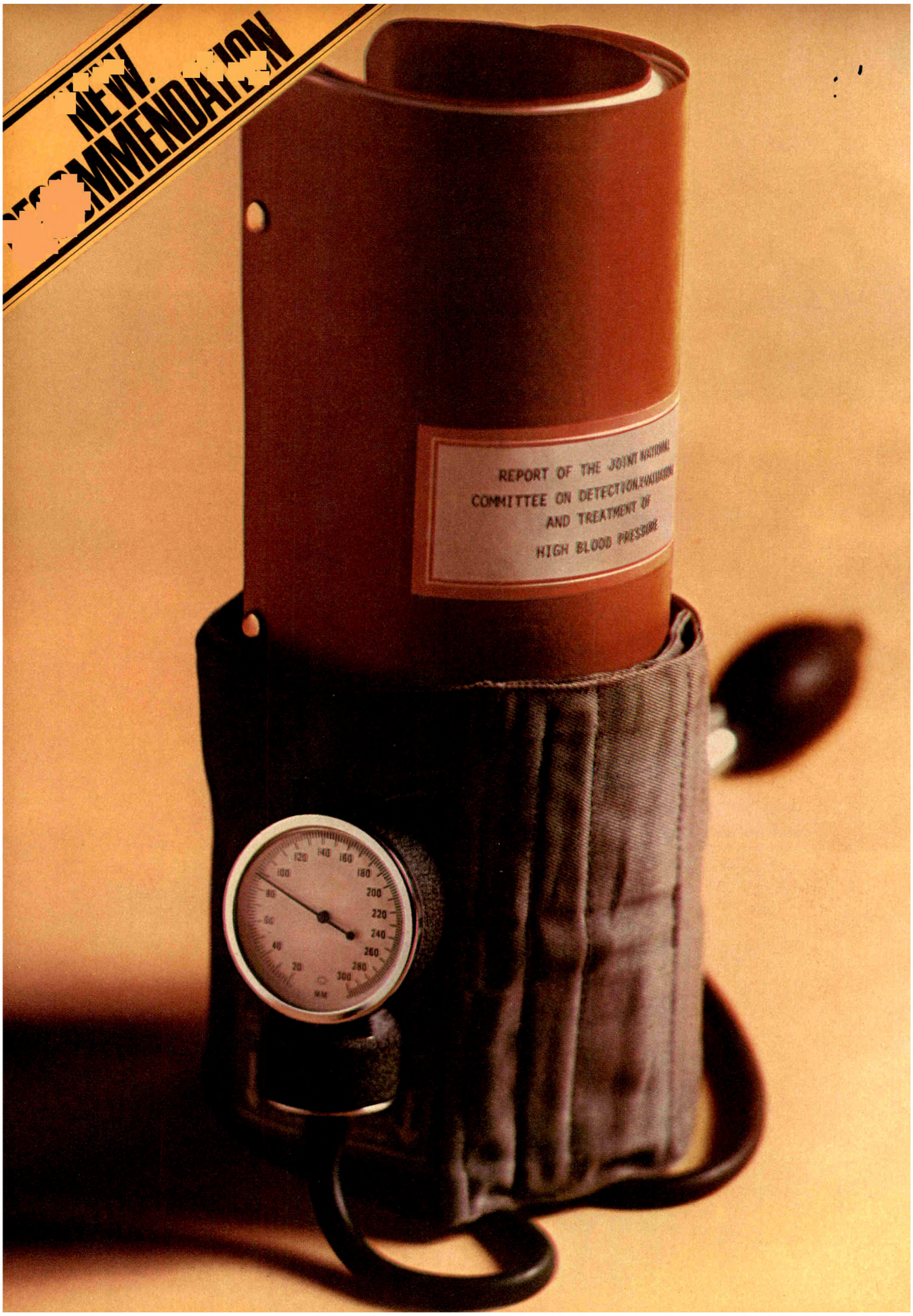
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CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency, usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

ORAL

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 40 mg INDERAL twice daily, whether used alone or added to a diuretic. Dosage may be increased gradually until adequate blood pressure is achieved. The usual dosage is 160 to 480 mg per day. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower doses are used, may experience a modest rise in blood pressure toward the end of the 12 hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or 3 times daily therapy may achieve better control.

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

INTRAVENOUS

The intravenous administration of INDERAL has not been evaluated adequately in the management of hypertensive emergencies.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg). IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS.

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE).

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

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No. 464—Each scored tablet contains 40 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

No. 468—Each scored tablet contains 80 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

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No. 3265—Each ml contains 1 mg of propranolol hydrochloride in Water for Injection. The pH is adjusted with citric acid. Supplied as: 1 ml ampuls in boxes of 10.

REFERENCE

Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,: Arch. Intern. Med. *140*:1280 (Oct.) 1980.

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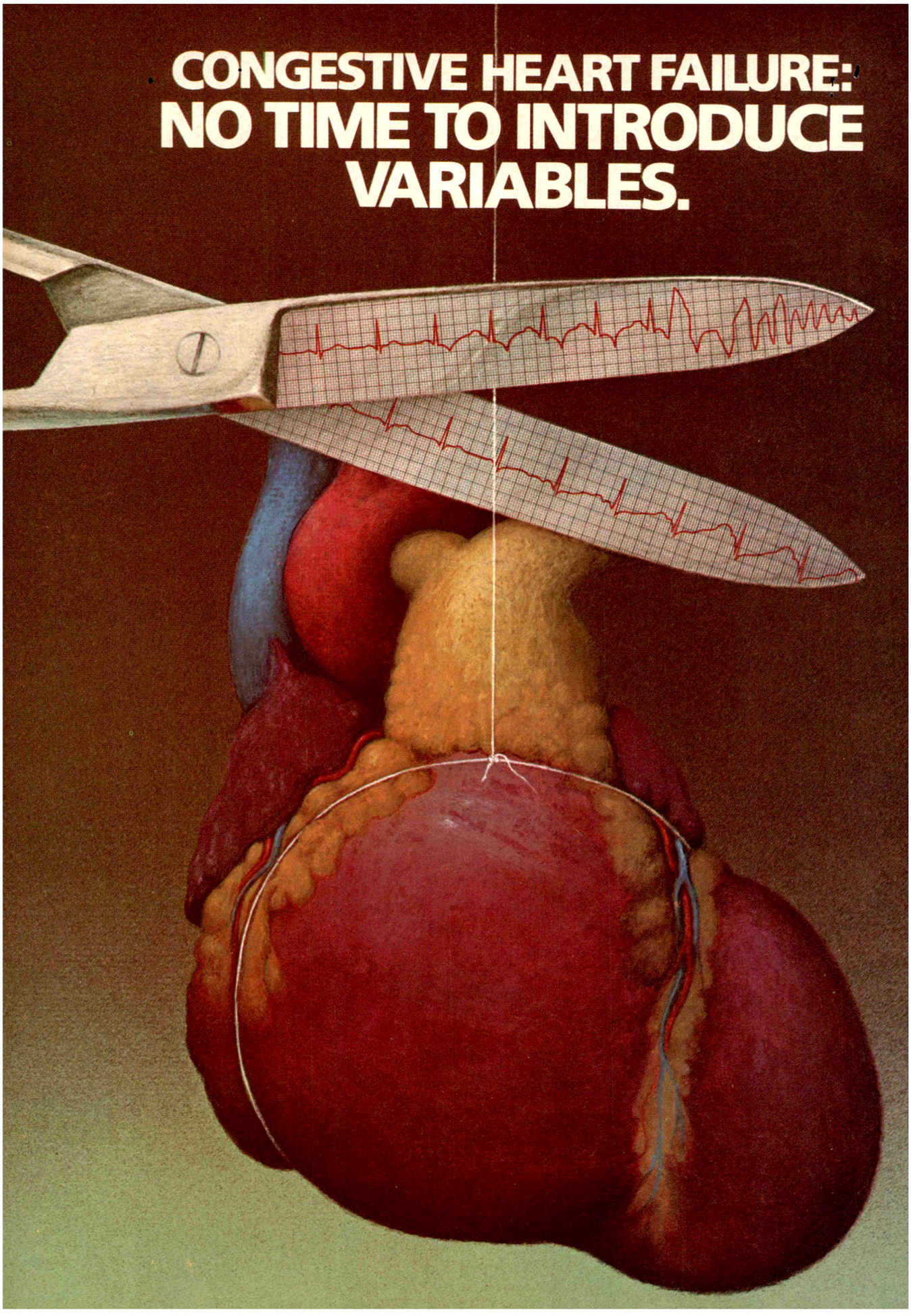

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References: 1. Moe GK, Farah AE: Digitalis and allied cardiac glycosides, in Goodman LS and Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co, 1970, pp 653-682. 2. Smith TW: Digitalis: Ions, inotropy and toxicity, editorial. *N. Engl. J. Med. 299*:545, 1978. 3. Rubinstein MH, Eastwood BA, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: The effect of lubricant type and concentration on the bioavailability of furosemide from 80 mg tablets: *J. Pharm. Pharmacol. 30* (suppl.):12P, Dec. 1978. 4. Rubinstein MH, Price EF, School of Pharmacy, Liverpool Polytechnic, Liverpool L3 3AF, U.K.: In vivo evaluation of the effect of five disintegrants on the bioavailability of furosemide from 40 mg tablets: *J. Pharm. Pharmacol. 29* (Suppl.):5P, Dec. 1977. 5. Rubinstein MH, Rughani JM, School of Pharmacy, Liverpool Polytechnic, Byrom Street, Liverpool L3 3AF, U.K.: The effect of four tablet binders on the bioavailability of furosemide from 40 mg tablets: *Drug Development and Industrial Pharmacy* 4(6): 541-553 (1978). 6. HEW News, publication 79-6, U.S. Department of Health, Education and Welfare (Food and Drug Administration), March 30, 1979, pp 2-3.

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A brief summary of the Prescribing Information for Lasix (furosemide). Tablets 20, 40 and 80 mg.

WARNING: Lasix (furosemide) is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required, and dose and dose schedule have to be adjusted to the individual patient's needs.

INDICATIONS: Edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Hypertension when used alone or in combination with other antihypertensive drugs; patients not adequately controlled with thiazides also probably will not be adequately controlled with furosemide alone.

CONTRAINDICATIONS: Because animal reproductive studies have shown that furosemide may cause fetal abnormalities, the drug is contraindicated in women of childbearing potential. Anuria. History of hypersensitivity to the compound.

WARNINGS: Excessive diuresis may result in dehydration and reduction in blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism, particularly in elderly patients. Excessive loss of potassium in patients receiving digitalis glycosides may precipitate digitalis toxicity. Exercise care in patients receiving potassium-depleting steroids. Perform frequent serum electrolyte, CO_2, and BUN determinations during first few months of therapy and periodically thereafter; and correct abnormalities or temporarily withdraw the drug. Initial therapy of patients with hepatic cirrhosis and ascites is best carried out in the hospital. Closely observe cirrhotic patients for sudden fluid and electrolyte imbalances that may precipitate hepatic coma. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis. Discontinue furosemide if increasing azotemia and oliguria occur during treatment of severe, progressive renal disease. Observe patients regularly for possible blood dyscrasias, liver damage, or other idiosyncratic reactions. Patients with known sulfonamide sensitivity may show allergic reactions. Furosemide may potentiate the therapeutic effect of other antihypertensive agents. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Exacerbation or activation of systemic lupus erythematosus may occur. Furosemide appears in breast milk. If use of the drug is essential, the patient should stop nursing. Cases of tinnitus and reversible hearing impairment have been reported.

There have also been some reports of cases in which irreversible hearing impairment occurred. Usually ototoxicity has been reported when furosemide was injected rapidly in patients with severe impairment of renal function at doses exceeding several times the usual recommended dose and in whom other drugs known to be ototoxic were given. If the physician elects to use high-dose parenteral therapy in patients with severely impaired renal function, controlled intravenous infusion is advisable. (For adults, an infusion rate not exceeding 4 mg furosemide per minute has been used.)

PRECAUTIONS: As with any effective diuretic, electrolyte depletion may occur, especially in patients receiving higher doses and a restricted salt intake. Patients receiving furosemide should be observed for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with furosemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis may exaggerate metabolic effects of hypokalemia, especially with reference to myocardial activity. Asymptomatic hyperuricemia can occur and gout may rarely be precipitated. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported. Furosemide may lower serum calcium levels, and rare cases of tetany have been reported. Periodic serum calcium levels should be obtained. Reversible elevations of BUN may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency. Patients receiving high doses of salicylates in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites. Furosemide has a tendency to antagonize the effects of tubocurarine and may potentiate the action of succinylcholine. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. Diuretics such as furosemide may enhance the nephrotoxicity of cephaloridine. Therefore, furosemide and cephaloridine should not be administered simultaneously. Furosemide may decrease arterial responsiveness to norepinephrine. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

It has been reported in the literature that coadministration of indomethacin may reduce the natriuretic and antihypertensive effects of Lasix (furosemide) in some patients. This effect has been attributed to inhibition of prostaglandin synthesis by indomethacin. Indomethacin may also affect plasma renin levels and aldosterone excretion; this should be borne in mind when a renin profile is evaluated in hypertensive patients. Patients receiving both indomethacin and Lasix (furosemide) should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Lasix (furosemide) is achieved.

ADVERSE REACTIONS: Anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia, blurred vision, tinnitus and hearing loss, anemia, leukopenia, agranulocytosis (rare), thrombocytopenia, aplastic anemia (rare), purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, pruritus. Orthostatic hypotension may occur and may be exaggerated by alcohol, barbiturates, or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis.

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Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

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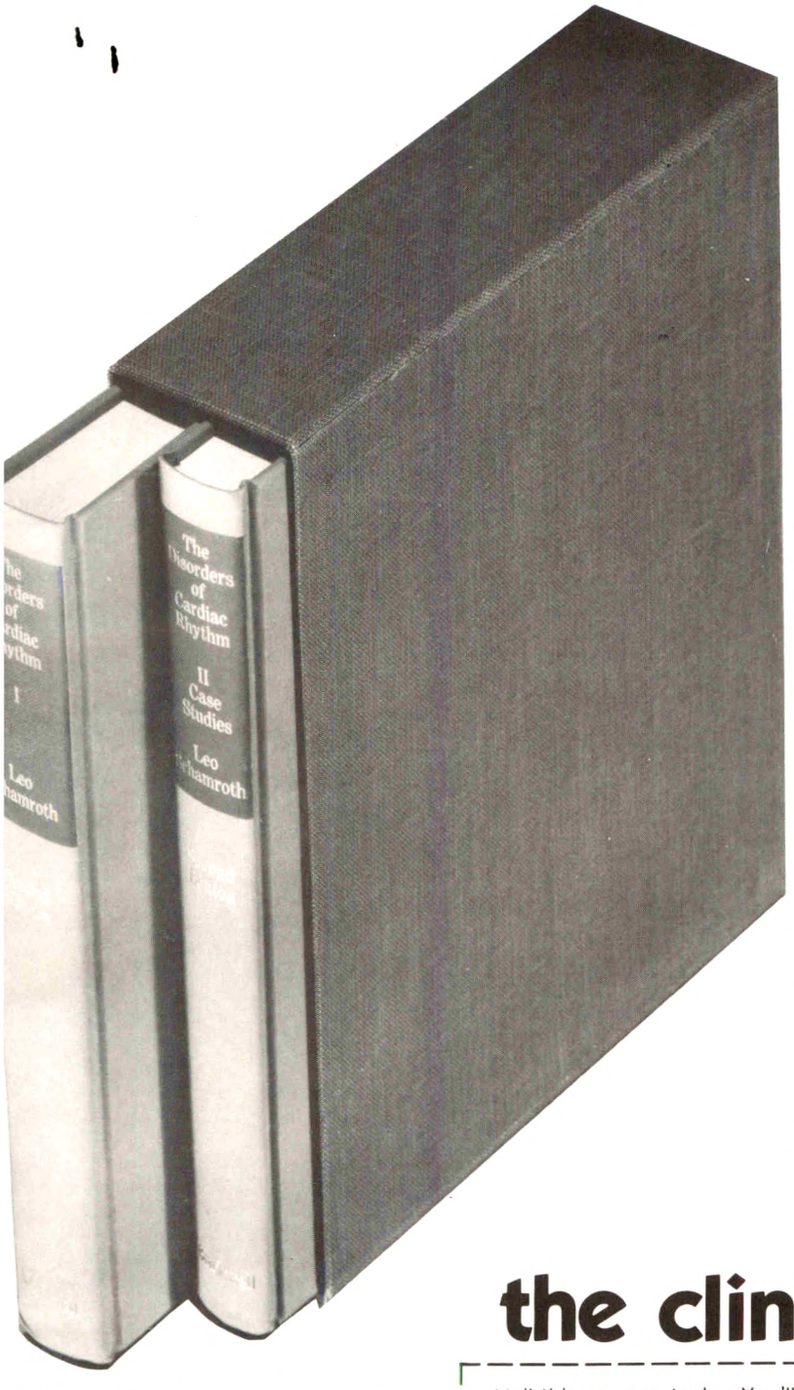

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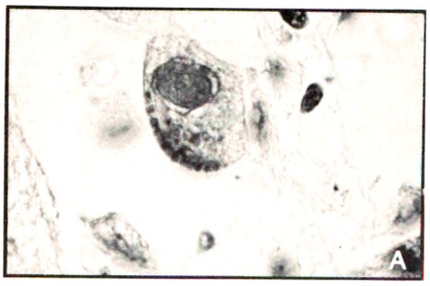

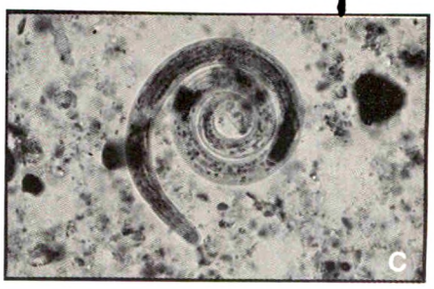

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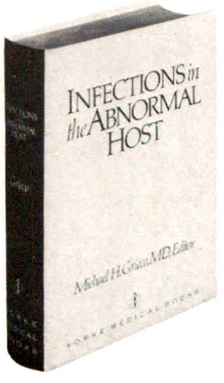

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Accuracy of Systolic Time Intervals in Detecting Abnormal Left Ventricular Performance in Coronary Artery Disease

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Sixty-six consecutive patients with a history of previous myocardial infarction and 48 patients with angina pectoris without evidence of previous myocardial infarction, all of whom had diagnostic coronary arteriography and left ventriculography, were studied in a prospective analysis of the accuracy of noninvasively determined systolic time intervals as a measure of global left ventricular performance. Forty-one patients who were evaluated for atypical chest pain and found to have normal coronary arteries and left ventricular performance served as control subjects. Six methods of statistical analysis were employed in assessing the accuracy of systolic time intervals in relation to the left ventricular ejection fraction: (1) analysis of variance, (2) cumulative distribution analysis, (3) correlation, (4) sensitivity and specificity, (5) percent agreement, and (6) logistic regression analysis. These tests permitted comparison between the systolic time intervals and the angiographic left ventricular ejection fraction. Analysis of variance revealed identical discriminating power for the ratio of the preejection period to left ventricular ejection time (PEP/LVET) and left ventricular ejection fraction in separating the normal group and patients without previous myocardial infarction from the patients with previous myocardial infarction. The preejection period and left ventricular ejection time corrected for heart rate were less discriminating than left ventricular ejection fraction or PEP/LVET. The cumulative distribution plots for the left ventricular ejection fraction and PEP/LVET in the three groups of patients were remarkably similar. The correlation of PEP/LVET and left ventricular ejection fraction for all three groups of patients was 0.84. The sensitivity and specificity of the PEP/LVET in relation to the left ventricular ejection fraction were 88 and 96 percent, respectively. The overall agreement between the two measures in detecting the prevalence of abnormality in global left ventricular performance in subgroups of patients was 92 percent. By logistic regression analysis the two measures had equal capacity in discriminating the patients with previous myocardial infarction from the control group.

The multiple strategies of comparison employed in this study document the close relation of measures of the timing of the left ventricular contraction cycle by systolic time intervals and estimates of the extent of left ventricular contraction by ejection fraction in patients with coronary artery disease. It is concluded that these measures afford independent and complementary methods of defining the presence of abnormal left ventricular performance in the resting supine patient with coronary artery disease.

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Systolic time intervals have been shown to be useful noninvasive measures of global left ventricular performance in various disease states.[1–5] However, there has been some controversy regarding the accuracy of systolic time intervals in patients with coronary artery disease. Some investigators[6–9] have been unable to demonstrate a close correlation between systolic time intervals derived with various methods and other established clinical measures of left ventricular performance. Other

studies[10] have found a remarkably high incidence rate of abnormal systolic time interval measurements in asymptomatic patients with stable coronary artery disease who had no overt clinical evidence of cardiac dysfunction on history or physical examination. These findings led to the following questions: Are systolic time intervals capable of discriminating between normal and abnormal left ventricular performance in a large group of patients with coronary artery disease and, if so, are the findings of abnormality by systolic time intervals clinically pertinent? The current prospective study on the accuracy of systolic time intervals was designed to answer these questions.

Methods

Study patients: Sixty-six consecutive patients who had a history of myocardial infarction and who were referred to our hemodynamics laboratory for evaluation of angina pectoris (Group II) and 48 consecutive patients who were admitted for coronary angiographic studies because of clinically evident angina pectoris and who had no evidence of previous myocardial infarction (Group III) were studied. All patients with myocardial infarction had recovered from the acute episode, which occurred at least 3 months before this study. Documentation of the infarction was established by (1) typical history of precordial chest discomfort, (2) characteristic serum enzyme changes, and (3) sequential evolution of electrocardiographic changes with persistence of pathologic Q waves. The patients without previous infarction had no history of prolonged precordial discomfort nor any electrocardiographic evidence of infarction. Both groups of patients with coronary artery disease were demonstrated to have 50 percent or greater narrowing of the diameter of at least one major coronary artery on coronary angiography. Forty-one patients who were referred for diagnosis of atypical precordial chest discomfort and who were later found to have normal coronary arterial and ventriculographic studies at cardiac catheterization (Group I) were used as control subjects.

Cardiac catheterization: Left ventricular end-diastolic pressure was obtained using retrograde catheterization of the left ventricle with a fluid-filled catheter system attached to a Statham P23Db pressure transducer. Left ventriculography was performed in the right anterior oblique position with 35 mm film at 30 frames/s utilizing a 9 inch (22.9 cm) image intensifier system with automated injection of Renovist® II (29 percent diatrizoate sodium and 28.5 percent diatrizoate meglumine). Left ventricular end-diastolic and end-systolic volumes were measured in the right anterior oblique position with the method of Green et al.[11] The ejection fraction was then calculated as the end-diastolic volume minus the end-systolic volume divided by the end-diastolic volume.[12,13] The ejection fraction determined in this manner by the single plane method is the most commonly employed clinical standard for detecting normal and abnormal resting supine left ventricular performance in patients with coronary artery disease. Selective coronary cinearteriography was performed in the right and left anterior oblique positions using either the Sones or Judkins technique with manual injection of Renografin®-76 (10 percent diatrizoate sodium and 66 percent diatrizoate meglumine) at 60 frames/s.

Systolic time intervals: These intervals were measured as previously described using simultaneous electrocardiographic, phonocardiographic and carotid arterial pulse tracings recorded photographically at 100 mm/s with an Electronics for Medicine VR-6 system.[1,2] For the electrocardiographic recording the lead most clearly delineating the onset of ventricular depolarization was used. For the phonocardiographic recording a contact microphone (EFM model, PSA 23, 1.5 cm disk) was placed over the upper portion of the precordium in the optimal position for recording the initial high frequency vibrations of the second heart sound. A frequency band of 100 to 500 hertz was used for this purpose. The carotid arterial pulsation was recorded using a funnel-shaped pickup (diameter 2.3 cm) connected by a short length of polyethylene tubing (length 8 cm, internal diameter 2 mm) to a Statham P23Db strain gauge.

Two phases of the cardiac cycle were measured directly: total electromechanical systole ($Q\text{-}S_2$) and left ventricular ejection time (LVET). The $Q\text{-}S_2$ interval was measured from the onset of ventricular depolarization on the electrocardiogram to the beginning of the initial high frequency component of the second heart sound in the phonocardiogram. The LVET was measured from the beginning of the upstroke to the trough of the incisural notch of the carotid arterial pulse tracing. The left ventricular preejection period was derived by subtracting left ventricular ejection time from the $Q\text{-}S_2$ interval. All intervals were calculated as the mean of measurements from 10 consecutive beats, each read to the nearest 5 ms. Left ventricular ejection time and preejection period measurement were corrected for heart rate using previously reported linear regression equations and were expressed as their respective indexes.[1,2,4] The ratio of PEP/LVET was calculated using the uncorrected values for prejection period and left ventricular ejection time.

Statistical analysis: This was performed with the aid of an IBM 370/165 computer located at Triangle Universities Computation Center, Research Triangle Park, North Carolina. Six methods of statistical analysis were employed in assessing the accuracy of the systolic time intervals in relation to the ejection fraction: (1) Kruskal-Wallis analysis of variance, (2) cumulative distribution analysis, (3) Pearson product-moment correlation, (4) sensitivity and specificity, (5) percent agreement, and (6) logistic regression analysis. These tests where chosen because they allow direct comparison of the systolic time intervals with the angiographic ejection fraction in characterizing left ventricular performance in both normal and abnormal populations of patients. Second, these methods are distribution-free and do not depend on a Gaussian distribution for the statistical validity of the comparisons. The use of parametric tests in non-normally distributed populations can lead to significant errors in interpretation of results.[14,15] The Kruskal-Wallis nonparametric analysis of variance procedure allows one to test for differences in the distribution of the systolic time intervals and ejection fraction among patient groups. The cumulative distribution plot allows a direct visual impression of the distribution of all data in each group. The ability of each test of ventricular performance to characterize the normal and abnormal populations can thus be readily appreciated. The Pearson correlation indicates the strength of the association between the systolic time interval and ejection fraction measurements among all patients. The sensitivity, specificity and percent agreement allow one to compare the systolic time intervals with the ejection fraction, assuming that the angiographically determined ejection fraction is able to categorize patients correctly as having either normal or abnormal left ventricular performance. The sensitivity as applied to the systolic time intervals is defined as the percent of abnormal patients (by ejection fraction) detected correctly, while the specificity is defined as the percent of normal patients correctly identified. The percent agreement is simply the number of patients with concordant abnormality by both tests plus the number of

TABLE 1

Mean, Median and Quartile Data for Left Ventricular Ejection Fraction and Systolic Time Intervals in Three Groups of Patients*

	Group I: Controls (n = 41)				Group II: CAD without MI (n = 48)				Group III: CAD with MI (n = 66)				I vs. II		II vs. III		I vs. III	
	Mean ±SD	Med 50%	Q_1 25%	Q_3 75%	Mean ±SD	Med 50%	Q_1 25%	Q_3 75%	Mean ±SD	Med 50%	Q_1 25%	Q_3 75%	χ^2	p	χ^2	p	χ^2	p
LVEF	69 ± 8	70	63	74	70 ± 7	70	65	75	47 ± 18	48	32	59	1.34	0.25	50.2	<0.0001	42.5	<0.0001
PEP/LVET	0.34 ± 0.04	0.33	0.32	0.36	0.35 ± 0.04	0.35	0.32	0.39	0.45 ± 0.09	0.44	0.38	0.52	2.54	0.11	35.4	<0.0001	42.9	<0.0001
PEPI	129 ± 13	128	122	140	129 ±12	128	119	140	148 ± 17	146	136	162	0	0.99	33.2	<0.0001	28.9	<0.0001
LVETI	410 ± 25	411	401	422	405 ± 16	408	395	414	391 ± 19	390	375	402	3.97	0.046	17.1	<0.0001	27.5	<0.0001

* Comparison of group data by analysis of variance.

CAD = coronary artery disease; LVEF = left ventricular ejection fraction; LVET = left ventricular ejection time; LVETI = left ventricular ejection time index; MED = median; MI = myocardial infarction; p = probability; PEP = preejection period; PEPI = preejection period index; Q = quartile; SD = standard deviation.

patients with concordant normality divided by the total number of patients expressed in percent. The logistic regression analysis allows comparison of the ability of ejection fraction and systolic time intervals to separate independently normal patients from those with previous myocardial infarction on the basis of left ventricular performance alone.

It should be emphasized that a prospective approach was used in selecting patients for study. Consecutive patients referred to the hemodynamics laboratory for catheterization had noninvasive evaluation within 48 hours of catheterization. The measurement of the systolic time intervals and ejection fraction was made independently and in separate laboratories by different workers, each uninformed of the corresponding data in the other laboratory.

Results

PEP/LVET versus ejection fraction: The mean, median and quartile data for left ventricular ejection fraction (LVEF), PEP/LVET, preejection period index (PEPI) and left ventricular ejection time index (LVETI) for all three groups of patients (control [Group I], coronary artery disease without myocardial infarction [Group II] and coronary artery disease with myocardial infarction [Group III]) are summarized in Table I. A curve-fitting technique was used to compare the distribution of the data in each of the groups to an ideal Gaussian distribution. The data for both PEP/LVET and ejection fraction in the 41 normal subjects were shown to have a Gaussian distribution so that the normal range for both variables was taken as the mean ± 2 standard deviations. Thus the upper limit of normal for PEP/LVET was 0.42, and the lower limit of normal for the angiographic ejection fraction was 53 percent. These data correspond to previously established norms for each variable.[1,11] The distribution of the data among patients with previous myocardial infarction, however, was significantly different from a Gaussian distribution for both ejection fraction ($p = 0.01$) and PEP/LVET ($p = 0.04$). Thus all further statistical comparisons utilized distribution-free nonparametric analysis.

The last three columns in Table I show the chi-square and probability (p) values for all variables using the Kruskal-Wallis nonparametric analysis of variance. The chi-square values for the comparison of the normal group to the patients with coronary artery disease but without infarction were quite small, demonstrating the absence of a significant difference in left ventricular performance in the two groups. The chi-square values for the comparison between the normal group and the patients with coronary artery disease and previous infarction were large and highly significant for all variables. It is of interest to note that the chi-square values for ejection fraction and PEP/LVET were close in magnitude (42.5 and 42.9, respectively), demonstrating a similar discriminating power in separating the normal patients from those with previous infarction. The preejection period and left ventricular ejection time indexes were also able to separate these groups but had lower chi-square values, indicating a somewhat lower discriminating capacity for distinguishing left ventricular dysfunction in patients with chronic coronary artery disease.

Cumulative distribution plots of the ejection fraction for each of the three groups are shown in Figure 1, and corresponding plots of PEP/LVET appear in Figure 2. The characterization of the left ventricular performance of each group by the ejection fraction was remarkably similar to that shown by the PEP/LVET. Patients with coronary artery disease without previous myocardial infarction appear very similar to the normal patients according to both variables, whereas the patients with previous infarction are quite distinct from the normal patients according to both PEP/LVET and ejection fraction. Thus, in the group comparisons, the invasive and noninvasive measures were very similar in the characterization of both the normal and the abnormal populations of patients.

The correlation of PEP/LVET and ejection fraction in all three groups of patients is shown in Figure 3. The

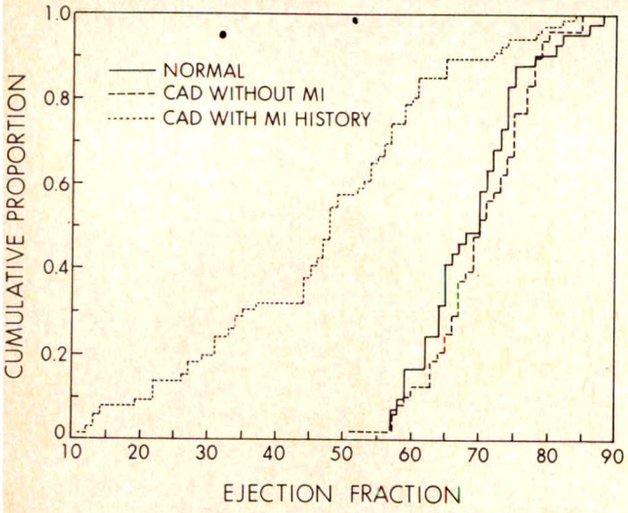


FIGURE 1. Cumulative distribution plot of the ejection fraction in the normal patients (**solid line**), those with coronary artery disease without myocardial infarction (CAD without MI) (**dashed line**) and those with coronary artery disease and previous myocardial infarction (CAD with MI history) (**dotted line**).

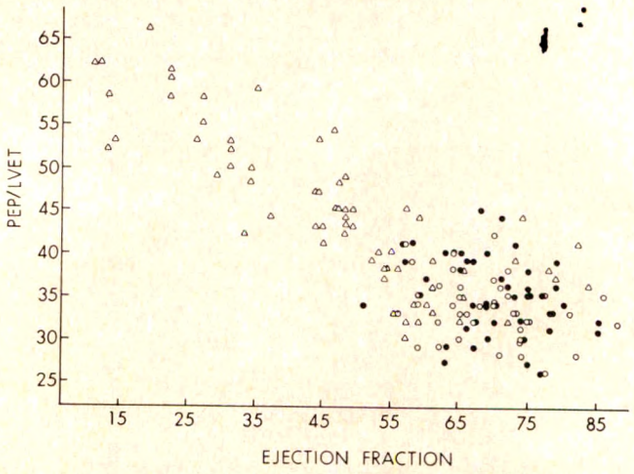


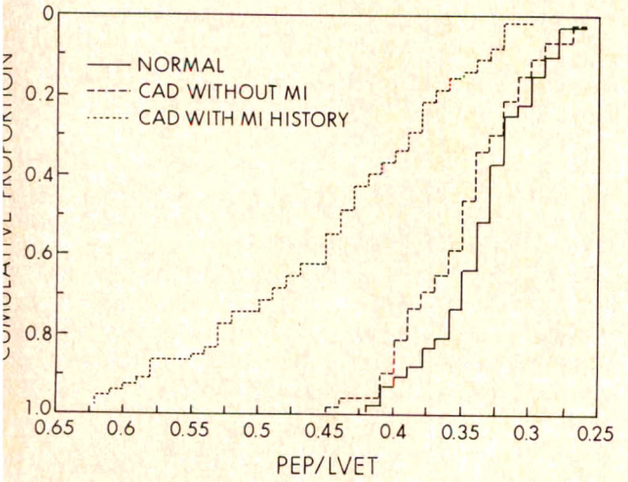
FIGURE 3. Correlation of PEP/LVET and ejection fraction in the normal patients (**open circles**), those with coronary artery disease without myocardial infarction (**closed circles**) and those with coronary artery disease and previous myocardial infarction (**open triangles**).

Pearson correlation coefficient was 0.84, demonstrating a high degree of correlation among the patients in all three groups.

Sensitivity and specificity of PEP/LVET: To approach the question of whether PEP/LVET could reliably separate patients with normal from those with abnormal left ventricular performance, we assumed temporarily that the angiographic ejection fraction could correctly separate patients with normal from those with abnormal left ventricular performance in all instances. We were then able to calculate the sensitivity and specificity of PEP/LVET for detecting abnormal and normal left ventricular performance, respectively (Fig. 4). The calculations were derived from the pooled data of control patients and both groups of patients with coronary artery disease using the 2 standard deviation limit of 0.42 for the PEP/LVET. The sensitivity (88 percent) and specificity (96 percent) confirm the accuracy of the PEP/LVET limit of 0.42 in detecting the presence of abnormal and normal left ventricular ejection fraction.

To test for the most clinically useful demarcation between normal and abnormal ventricular performance by PEP/LVET, the sensitivity and specificity over a large range of limits for PEP/LVET were determined (Fig. 5). It is apparent from the data display that the point of maximal combined sensitivity and specificity occurs at the crossover point of the sensitivity and specificity curves. This crossover corresponds almost exactly (0.41) to 2 standard deviations above the mean for PEP/LVET (0.42). At a limit of 0.45, the point of 100 percent specificity is reached. All patients with a normal angiographic ejection fraction had a PEP/LVET value below this point. Similarly, at a limit of 0.34 the point of 100 percent sensitivity is achieved. The data for all patients with an abnormal left ventricular ejection fraction were above this limit.

Prevalence of abnormality by both tests: As an additional test of the clinical applicability of the systolic time interval measurements compared with that of the ejection fraction, the prevalence of abnormality by both tests as well as the percent agreement between the two tests in detecting abnormal left ventricular performance in several clinical subsets of patients was determined. Table II summarizes the prevalence of abnormality and the degree of agreement between PEP/LVET and ejection fraction in subgroups designated according to degree of arterial obstruction on angiography (those with one, two and three vessel disease), the presence of



GURE 2. Cumulative distribution plot of the preejection period/left ntricular ejection time ratio (PEP/LVET) in the normal patients (**solid e**), those with coronary artery disease without myocardial infarction AD without MI) (**dashed line**) and those with coronary artery disease d previous myocardial infarction (CAD with MI history) (**dotted e**).

SENSITIVITY:

$$\frac{\text{TRUE POSITIVES (35)}}{\text{TRUE POSITIVES (35) + FALSE NEGATIVES (5)}} = 88\%$$

SPECIFICITY:

$$\frac{\text{TRUE NEGATIVES (110)}}{\text{TRUE NEGATIVES (110) + FALSE POSITIVES (5)}} = 96\%$$

FIGURE 4. Sensitivity and specificity of PEP/LVET in detecting the presence of abnormal (sensitivity) and normal (specificity) left ventricular ejection fraction.

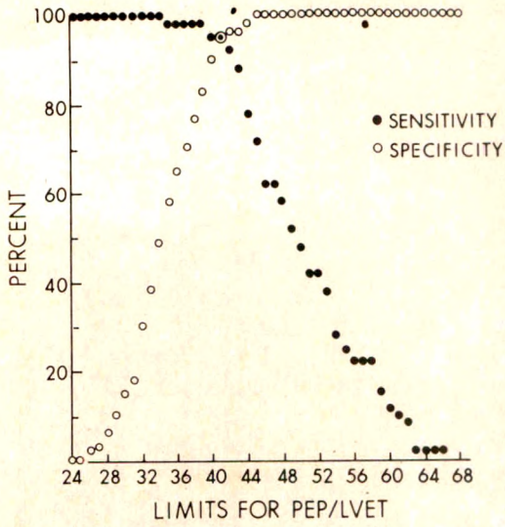


FIGURE 5. Sensitivity and specificity at various upper limits of normal for PEP/LVET. The sensitivity is denoted by **closed circles** and the specificity by **open circles.**

elevated end-diastolic pressure at cardiac catheterization and the presence or absence of previous infarction. A high degree of agreement between PEP/LVET and ejection fraction was demonstrated in these subgroups of patients with coronary artery disease.

Logistic regression analysis to discriminate between normal and abnormal populations: The final approach to the analysis of the accuracy of the systolic time intervals in separating normal from abnormal patients was the use of logistic regression analysis. In this procedure the ability of both tests to separate the patients who had had a documented previous myocardial infarction (Group II) from the normal (control, Group I) patients on the basis of left ventricular performance was examined. Although many patients have fully compensated ventricular performance after recovering from an infarction, it follows that a more sensitive test will be able to detect the more subtle degrees of residual functional impairement. Table III gives the chi-square and corresponding p values for the logistic regression analysis of PEP/LVET, ejection fraction, and PEP/LVET and ejection fraction combined, in discriminating between normal patients and those with previous infarction on the basis of left ventricular performance alone. When considered independently, both PEP/LVET and ejection fraction are able to discriminate between these groups. When both tests are combined and the results for each measure are adjusted for the effect of the other, both PEP/LVET and ejection fraction remain highly significant, indicating that each test contributes important independent information in discriminating between the normal and abnormal populations.

TABLE II

Comparison of PEP/LVET with Ejection Fraction in Detecting Abnormal Left Ventricular Performance

	n	Abnormal by LVEF (EF <0.53) (%)	Abnormal by PEP/LVET (PEP/LVET >0.42) (%)	% Agreement*
Vessels involved (n) (>50% diameter narrowing)				
1	27	22	22	93
2	29	14	14	100
3	58	50	52	88
End-diastolic pressure (mm Hg)				
≤14	80	24	25	91
>14	34	62	59	97
Myocardial infarction				
CAD without MI	48	2	4	94
CAD with MI	66	58	58	91
All patients with CAD	114	34	35	92

* Patients (n) with concordant PEP/LVET and LVEF × 100/total patients.

Abbreviations as in Table I.

Discussion

The present study was designed to test the accuracy of systolic time intervals in detecting abnormal left ventricular performance in patients with stable coronary artery disease. The preejection period/left ventricular ejection time ratio (PEP/LVET) was compared with the angiographically determined left ventricular ejection fraction, the most commonly applied clinical laboratory standard for defining the presence of global left ventricular dysfunction. The study included a large number of patients with angiographically defined coronary artery disease, including patients with and

TABLE III

Discrimination Between Control Patients and Patients With Previous Myocardial Infarction Using Logistic Regression Analysis

	PEP/LVET or LVEF Alone		PEP/LVET and LVEF Combined	
	χ^2	p	χ^2	p
PEP/LVET	23.40	<0.0001	9.95	0.0016
LVEF	23.22	<0.0001	6.41	0.0114

Abbreviations as in Table I.

without previous myocardial infarction and encompassing a wide range of left ventricular performance. The statistical analysis was extended beyond correlation, the only statistical method used in all previous studies, since the latter does not provide a critical test of the accuracy of the systolic time intervals in differentiating normal from abnormal populations. A prospective analysis of consecutive patients referred for evaluation of coronary artery disease was used. The invasive and noninvasive data were acquired in independent laboratories by different technicians who were unaware of the results of the corresponding measurements.

Close correlation of changes in PEP/LVET and ejection fraction: The PEP/LVET, the ratio of preejection to ejection phase duration, like the ejection fraction, provides a measure of global performance of the left ventricle. The closeness of the changes in the PEP/LVET and the ejection fraction summarized in this study demonstrates a unique parallelism in the alteration of the timing of the events of the cardiac cycle with the decrease in the extent of chamber contraction that accompanies left ventricular dysfunction in coronary artery disease. When considered in relation to the difference in the physiologic events reflected in these methods, one a measure of timing and the other a measure of the extent of chamber contraction, the two determinations must be considered complementary indexes of the left ventricular contractile dysfunction that accompanies coronary artery disease.

Limitations of previous correlative studies: Previous investigations[6–9] correlating systolic time intervals with left ventricular ejection fraction have not consistently demonstrated r values for the relation between PEP/LVET and ejection fraction as high as that reported previously from our laboratory[5] or in the present study. However, the methods used to measure the systolic intervals in those studies differ from that described in our original investigations on systolic time intervals.[1,2] Thus, in three of the studies[6,8,9] only five complexes were employed for measuring the intervals despite admonitions[1,2,4] that a larger number of consecutive beats (at least 10) should be measured to obtain acceptable accuracy in measuring systolic time intervals. Further, the use of crystal transducers[6,9] and a glycerin pellet[7] without verification of their frequency response or time constant could account for major variations in the measurements in these studies. In one study[7] a computer approach to measuring systolic time intervals was employed as well. The correlation between the computer- and hand-measured preejection period, the measurement that encompasses all four landmarks employed in the measurement of systolic time intervals, was 0.85. This level of correlation itself imposes a lower correlation between PEP/LVET and ejection fraction than can be derived by technician-measured systolic time intervals, the approach employed in the present and all other previous studies. In addition, the same study[7] included 82 patients with complicating disorders in addition to coronary artery disease, particularly mitral regurgitation, which has been shown to increase PEP/LVET above the level caused by abnormal left ventricular performance.[17]

The failure to include data on normal subjects by which one could compare methodologic approaches in three of the studies[7–9] makes it impossible to assess the magnitude of the differences in measurements that these methodologic variations might have imposed. The one study that did use normal control subjects[6] suggests that these alterations in equipment and methods are indeed important. The upper limit of normal for PEP/LVET in that study was 0.48, a level that is well into the abnormal range when standard methods are employed. In two independent reports by Lewis and co-workers[4,17] in which methods identical to that used in this study were employed, correlations between PEP/LVET and left ventricular ejection fraction were 0.85 and 0.76, respectively, in patients with chronic coronary artery disease. The r values in these reports do not differ significantly from that in the present investigation. Thus there was close agreement in all correlation studies employing methods of determining the systolic time intervals identical to that reported in the present study. Major reductions in the r values were observed in the studies in which methodologic differences were introduced into the systolic time interval determinations. Thus, methodologic variations offer the most plausible explanation for the differences in closeness of fit between ejection fraction and PEP/LVET data in these previously reported studies.[6–9]

PEP/LVET versus ejection fraction to detect left ventricular dysfunction: The group analysis of the data in the current study permitted comparison of the capacity of PEP/LVET and left ventricular ejection fraction to separate patients with normal performance from those with left ventricular dysfunction. Among the patients with coronary artery disease with and without previous myocardial infarction, the PEP/LVET proved equivalent to the ejection fraction in identifying the patients with abnormal left ventricular performance. The specificity and sensitivity calculations permitted a test of the accuracy of PEP/LVET in detecting the presence of a normal and abnormal ejection fraction among the pooled population of patients with and without coronary artery disease. This form of data analysis was selected in order to approach the question of the clinical applicability of PEP/LVET measurements in identifying patients with abnormal and normal ventricular performance by angiographic ejection fraction among a mixed population of patients. Clearly, the high degree of specificity and sensitivity denotes that an abnormal PEP/LVET predicts the presence of an abnormal ejection fraction, and its significance in clinical interpretation would be similar to that of the latter. The calculation of the percent agreement between the two measures in detecting the presence of left ventricular dysfunction in the clinical subgroups of patients validates the use of PEP/LVET in segregating subpopulations of patients with abnormal left ventricular performance. The presence of an abnormal ejection fraction in patients with more extensive coronary arterial obstruction and with high end-diastolic pressure

was detected with a high degree of accuracy by the measurement of PEP/LVET. The use of the nonparametric and logistic regression analysis permitted precise comparison and subsequent independent analysis of both PEP/LVET and ejection fraction in this nonnormally distributed patient population.

Clinical implications: The studies summarized herein reflect the virtual equivalence of the PEP/LVET and the angiographically determined ejection fraction in defining the presence of normal or abnormal left ventricular performance in the resting supine patient with coronary artery disease. On the basis of the group data analysis, the high level of correlation, the high degree of specificity and sensitivity of PEP/LVET in defining normal and abnormal data points for left ventricular ejection fraction, the agreement in clinical subsets of patients, and logistic regression analysis, it can be concluded that PEP/LVET affords an accurate expression of the global performance of the left ventricle in coronary artery disease. The agreement between this noninvasive estimate of left ventricular performance and the ejection fraction measurement in individual patients supports the application of systolic time intervals as a readily obtainable and reliable clinical measure of left ventricular performance when methodologic standards are maintained. The safety, reliability and easy accessibility of the systolic time intervals suggests their application in future clinical studies on factors influencing left ventricular performance in coronary artery disease.

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Noninvasive Detection of Left Ventricular Dysfunction With A Portable Electrocardiographic Gated Scintillation Probe Device

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A comparison of left ventricular function data derived from a low cost, portable electrocardiographic gated scintillation probe (nuclear stethoscope) with conventional scintiangiographic data was performed in 68 patients. Ejection fraction correlation ($r = 0.86$, $p < 0.005$) was better in patients with uniform wall motion than in those with regional asynergy ($r = 0.68$ $p < 0.01$). Probe variables reflecting systolic emptying rates, diastolic filling rates and timing intervals, and relative volumes analyzed in combination provided 100 percent sensitivity, specificity, and predictive value in detecting abnormal left ventricular performance. The results suggest that radionuclide angiography with an electrocardiographic gated scintillation probe is a sensitive, rapid and relatively inexpensive portable method of screening for cardiac dysfunction with a yield similar to that from the more costly gamma camera derived scintiangiogram.

Nonimaging electrocardiographic gated radiation detection systems have been utilized for more than 30 years to provide clinically useful noninvasive measurements of cardiac function.[1] Radiocardiograms from low temporal resolution scintigraphic probe systems (0.5 second per data point) were first used to derive cardiac output, pulmonary transit times and intracardiac shunts.[2–9] With the development of higher temporal sampling probe systems, ejection fraction could be derived from these first transit radiocardiograms.[10] The advent of scintigraphic gamma camera imaging systems, electrocardiographic gating, and sophisticated minicomputers dedicated to the production of dynamic cardiac blood pool imaging has made possible scintigraphic qualitative assessment of cardiac wall motion. Analysis of sequential count data in a spatially defined area of interest from numerous aggregated cardiac cycles can then be performed. A representative single cardiac cycle time-activity (volume) curve results, from which quantification of ejection fraction, volumes and other function variables can be derived.[11,12]

Although these elaborate dynamic cardiac imaging systems provide clinically useful data, their cost is great in terms of equipment and specially trained manpower required. Spatial imaging requires human and computer processing of data that often delays the immediate availability of scintiangiographic results. Substitution of temporal for spatial resolution (time-activity curve quantification rather than dynamic heart imaging) utilizing electrocardiographic gated scintillation probe devices allows approximately a 10-fold reduction in size and expense when compared with conventional imaging gamma cameras. An electrocardiographic gated scintillation probe device incoporating new microprocessor technology enables acquisition, calculations and display of results virtually instantaneously after proper placement of the probe with a separate imaging system.[13] Another probe system, the Nuclear Stethoscope (Bios, Valhalla, New York), incorporates such microprocessor technology with a unique positioning strategy to locate the left

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ventricular cavity in an otherwise position-blind electrocardiographic gated scintillation probe device.[14–16] This report compares the findings of this portable system with those from the more elaborate and expensive dynamic heart imaging system in the detection of left ventricular dysfunction.

Methods

The nuclear stethoscope: A unique gamma scintillation probe, the nuclear stethoscope, consisting of an electrocardiographic gated scintillation probe and dedicated microprocessor, combines a 2 inch (5 cm) thallium drifted sodium iodide detector with a converging collimator designed to give a 2.75 inch field of view at the focal plane of the heart 1.5 inches from the face of the collimator when placed on the chest wall over the precordium. It contains an Intel 8085 microprocessor programmed to measure, calculate and display data in real time over a 256 by 256 element matrix utilizing 6K programmable and 4K random access memory. Monitoring modes utilize an electrocardiographic gating system designed to sense R waves and reject premature beats. Noise artifact is automatically filtered out. The beat to beat position monitor mode allows analysis of individual beats and a positioning algorithm strategy. In this mode, the microprocessor provides an independent means of identifying the optimal sites for both left ventricular and background sampling. The electrocardiographic dependent positioning algorithms are designed to detect regions of interest demonstrating maximal stroke volume as well as to differentiate between right and left ventricular end-diastolic volumes. The background site is also detected by a positioning algorithm that is maximally satisfied when stroke volume is minimal and out of synchronization with the electrocardiographic signal. Background is then automatically subtracted before analysis of data to compensate for "false" information contributed by contiguous isotope-containing structures.

Study patients: Sixty-eight patients were referred for diagnostic imaging because of known or suspected heart disease. All patients had Anger camera and nuclear stethoscope studies in random order, performed independently by different technicians in separate rooms following administration of 15 to 20 mCi technetium-99m–labeled human serum albumin. Routine blood pool imaging, using an Ohio Nuclear Camera-V.I.P. 550 system in anterior and 30° left anterior oblique views, was obtained as a basis for comparison with the probe data. Left ventricular ejection fraction in the 30° left anterior oblique view was quantitated and wall motion in both views was qualitatively assessed with use of a previously validated methodology.[17] Abnormal cardiac function was defined as a left ventricular ejection fraction of less than 0.50 or a regional wall abnormality.

Analysis of data and calculations: All nuclear stethoscope data were analyzed by an experienced operator. Equilibrium mode monitoring of the patient's left ventricle was obtained in both beat to beat and gated ventricular function modes. The latter mode produced high fidelity left ventricular time-activity curves with 20,000 to 30,000 counts in the end-diastolic frame (aggregation of count data from 30 to 45 beats after a standard study dose of 15 mCi of technetium-labeled blood pool agent). The higher temporal resolution gated ventricular function mode (10 ms per data point) was selected over the lower temporal resolution beat to beat mode (50 ms per data point) for statistical analysis.

The following left ventricular indexes were obtained from the net left ventricular time-activity curves (Fig. 1), updated, and displayed by the nuclear stethoscope microprocessor in real time:

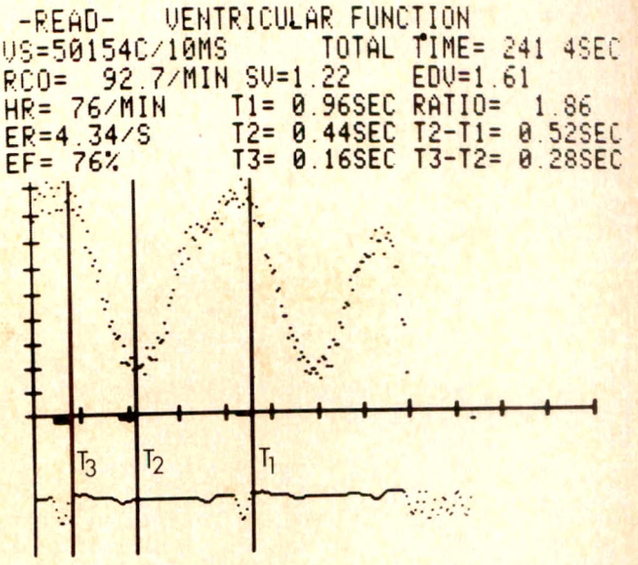

FIGURE 1. High temporal resolution left ventricular time-activity curve obtained by monitoring a blood pool radioisotope with a portable electrocardiographic gated scintillation probe device (nuclear stethoscope). Cardiac timing intervals, ejection fraction (EF), heart rate (HR), ejection rate (ER) and relative volumetric variables of stroke volume (SV) and end-diastolic volume (EDV) can be derived by microprocessor in real time from this typical display, providing immediate clinical data feedback. Cursors (T_3-T_2) have been placed by the operator to bracket the systolic ejection time and combined rapid and slow diastolic filling phases (T_2-T_1). Each data point represents a sampling time of 10 ms.

$$\text{Ejection fraction} = \frac{\text{End-diastolic counts} - \text{End-systolic counts}}{\text{End-diastolic counts} - \text{Background counts}} \quad (1)$$

$$\text{Relative stroke volume} = \frac{\text{End-diastolic counts} - \text{End-systolic counts}}{0.5\,\{(\text{End-diastolic counts} + \text{End-systolic counts}) - (\text{Background counts})\}}. \quad (2)$$

$$\text{Relative end-diastolic volume} = \frac{\text{End-diastolic counts}}{(0.5)\{(\text{End-diastolic counts} + \text{End-systolic counts}) - \text{Background counts}\}} \quad (3)$$

$$\text{Relative cardiac output} = \text{Heart rate} \times \text{Relative stroke value} \quad (4)$$

$$\text{Ejection rate} = \frac{\text{End-diastolic counts} - \text{End-systolic counts}}{(0.5)\{(\text{End-diastolic counts} + \text{End-systolic counts}) - \text{Background counts}\}} \times \frac{1}{\text{Left ventricular ejection time}}. \quad (5)$$

$$\text{Fast-filling rate} = \frac{\text{End-diastolic counts} - \text{End systolic counts}}{(0.5)\{(\text{End-diastolic counts} + \text{End-systolic counts}) - \text{Background counts}\}} \times \frac{1}{\text{Left ventricular fast filling time}}. \quad (6)$$

Relative volumetric variables (stroke volume and end-diastolic volume) could potentially be converted to absolute variables within this system by comparison with the absolute cardiac output derived in a separate nuclear stethoscope operating mode, the first transit mode. In first transit mode, monitoring a bolus injection as it passes through the heart provides a traditional radiocardiogram suitable for microprocessor derivation of absolute cardiac output by standard Hamilton-Stewart analysis. Comparison of the initial first transit cardiac output with subsequent monitoring mode relative cardiac output provides a calibration factor. This factor allows conversion of all subsequent gated monitoring mode relative volumetric variables to absolute terms. Relative variables are in units of counts per unit time, and absolute variables are in conventional units of milliliters per unit time. Relative volumetric variables were chosen for analysis to eliminate the necessity of an adequate bolus injection required in the first transit mode and subsequent conversion process.

The following temporal subdivisions of the cardiac cycle time-activity curve were displayed after operator placement of cursors (method of Qureshi et al.)[18]*:*

1. *Preejection period* = period of electromechanical delay and isovolumic contraction. This represents the initial plateau phase of the curve.
2. *Left ventricular ejection time* = period of ventricular emptying with onset at the first change in slope from the preejection period plateau and termination when the slope goes through zero at the nadir of the curve.
3. *Left ventricular fast filling time* = period of rapid ventricular filling after aortic valve closure. This period begins with protodiastolic cessation of ventricular ejection and concludes with the onset of left ventricular diastasis represented by a blunting of the upward slope of the curve.
4. *Left ventricular diastasis time including atrial systole* = slow phase of ventricular filling before the next systole, taken from the point where the rapid rise of ventricular filling suddenly slows to the end of the cardiac cycle.

In addition to this analysis, a rate-related analysis of each variable by dividing each subdivision of the time-activity curve by the total cycle time was performed and displayed in real time throughout the acquisition and recorded at the completion of the study. The average study required 10 to 20 minutes for completion. The optimal left ventricular site was generally 1 to 5 cm medial to the point of maximal impulse in a 30° to 40° left anterior oblique orientation with a 10° caudal tilt. The optimal background site was usually midway between the left ventricular apex and the spleen in the same left anterior oblique orientation.

Reproducibility: Results could be reproduced with less than 5 percent variation by using the positioning algorithm. All patients had duplicate studies with less than 5 percent difference in ejection fraction on consecutive probe placement and acquisition as well as serial repeated observations at the identical sampling site considered a valid collection. Acquisition was noted to be position-dependent: Displacement of the probe-chest orientation by 2 to 3 cm significantly altered results. A 30 case load experience produced uniform reproducibility, probably as a consequence of learned hand-eye coordination of algorithm-guided probe placement. The data in this study were acquired by a single operator whose experience included more than 200 cases.

Statistical analysis: Inference of significance in the various nuclear stethoscope variables was derived from a Student distribution analysis with two tails and represents at least a probability (p) value of <0.05 except as otherwise stated. Inference of significance for Y intercept values from regression analysis of ejection fractions is based on limits on predicted individual values assuming homoscedasticity as well as by the standard error of the estimate analysis on the Y intercept.

Results

Standard gamma camera imaging identified abnormalities in 50 patients (ejection fraction less than 0.50 or a regional wall motion abnormality) and normal findings (ejection fraction greater than 0.50 and normal wall motion) in 18. A decreased ejection fraction (less than 0.50) was found in 47 of the 50 patients in the abnormal group, and wall motion abnormalities were detected in 26 (52 percent). Of the 47 patients with a decreased ejection fraction, 23 (49 percent) had regional wall motion abnormalities. Three of the 50 patients (6 percent) had abnormal wall motion and a normal ejection fraction. There were no statistically significant differences in age or sex distribution in the normal and abnormal groups.

Effect of wall motion abnormalities on left ventricular ejection fraction: To evaluate the effect of localized wall motion abnormalities on nuclear stethoscope-determined left ventricular values, patients were grouped according to presence or absence of asynergy on standard gamma camera imaging. Group 1 consisted of 42 patients with uniform wall motion, either normal (Group Ia, n = 18) or diffusely hypokinetic (Group Ib, n = 24). Group II consisted of all patients with asynergy (n = 26). There was a good relation between ejection analysis from the gamma camera and those from the nuclear stethoscope in Group I ($r = 0.86$, $p < 0.005$) (Fig. 2A). Nuclear stethoscope and gamma camera comparison of left ventricular ejection fraction in Group II yielded a lower correlation ($r = 0.68$, $p < 0.01$) (Fig. 2B). Linear regression analysis revealed that the nuclear stethoscope-derived ejection fraction consistently overestimated gamma camera ejection fraction. This overestimation was significantly greater in Group II (patients with asynergy).

Background determination was analyzed in all patients. Mean background determination was 75 percent of maximal end-diastolic counts in Group Ia, 73 percent in Group Ib and 83 percent in Group II.

Analysis of left ventricular variables (sensitivity, specificity, predictive value): Mean, standard deviation and standard error of the mean were calculated for each nuclear stethoscope-derived variable of left ventricular function in both normal and abnormal groups. Standard error of the mean analysis was in turn used to calculate standard error of the difference for each value (Table I). This analysis revealed widest separation in the distribution of results in the normal and abnormal populations for the relative cardiac output, ejection rate, fast filling rate, the ejection fraction and the ejection fraction divided by the fast filling time. Confidence levels of 66.8 percent (mean less 1 standard deviation) and 95 percent (mean less 2 standard deviations) were determined for these values derived from Group Ia (patients with normal, uniform wall motion) and compared with results in the total group of patients with abnormalities (Group Ib, uniform diffuse hypo-

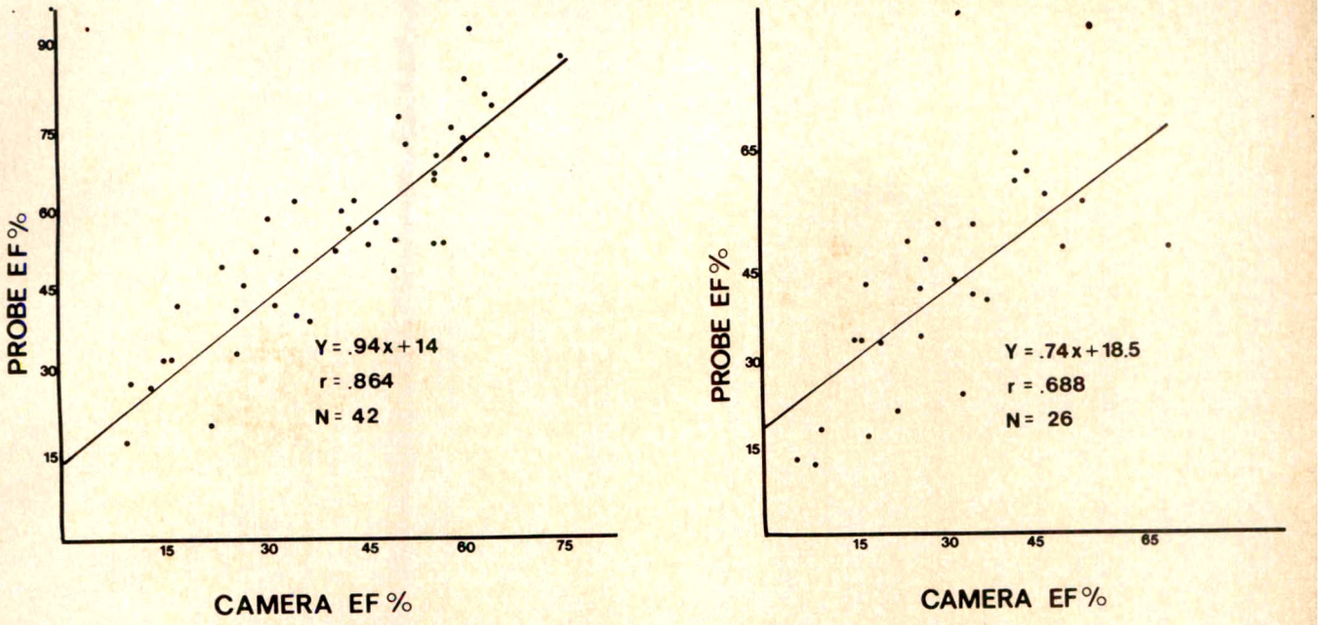

FIGURE 2. Linear regression analyses of ejection fraction (EF) measurements derived by the conventional Anger camera-computer system with those from the nuclear stethoscope probe system. **Left,** shows the correlation in the 42 patients determined by camera-computer–derived scintiangiogram to have uniform wall motion (normal [Group Ia] or diffusely hypokinetic [Group Ib]). **Right,** the poorer correlation in the 26 patients found by camera study to have regional left ventricular asynergy (Group II).

kinesia, and Group II, asynergy) (Fig. 3). Ninety-five percent confidence levels for the nuclear stethoscope-derived ejection fraction in the 50 abnormal patients predicted 44 (88 percent) patients with abnormality. When 66.8 percent confidence levels for the nuclear stethoscope variables in the normal group were defined as a cutoff value in separating normal from abnormal function, more sensitive variables for the detection of abnormal function emerged (ejection fraction 100 percent sensitivity, relative stroke volume 100 percent, relative end-diastolic volume 100 percent, relative cardiac output 98 percent, ejection rate 96 percent, fast filling rate 94 percent, ejection fraction divided by fast filling time 92 percent). Specificity was reduced in certain variables (relative cardiac output 100 percent, ejection rate 89 percent, fast filling rate 89 percent, ejection fraction divided by fast filling time 88 percent, relative stroke volume 83 percent, relative end-diastolic volume 83 percent, ejection fraction 83 percent). Predictive value analysis identified relative cardiac output (100 percent), ejection rate (96 percent), fast filling rate (96 percent), and ejection fraction divided by fast filling time (96 percent) as better individual measures of abnormal performance than ejection fraction (94 percent) (Table II). In all patients studied, any two of three of these nuclear stethoscope variables—relative cardiac output, ejection rate, fast filling rate or ejection fraction divided by fast filling time—falling above or below the 66.8 percent confidence level correctly identified all patients determined with the gamma camera to be in the normal or abnormal group (100 percent sensitivity, specificity and predictive value).

Discussion

Ejection fraction to monitor left ventricular function: Assessment of left ventricular function by ejection fraction and wall motion analysis with scintillation camera and dedicated computer correlates closely with cardiac catheterization results and has been widely accepted as a noninvasive method for evaluation of cardiovascular physiology.[17–27] The results of this study suggest that the nuclear stethoscope can effectively be used to detect left ventricular dysfunction by monitoring ejection fraction. Comparison of gamma camera and nuclear stethoscope ejection fraction measurements revealed excellent correlation in patients with uniform wall motion and acceptable correlation in patients with nonuniform wall motion. A small group of four patients with a depressed gamma camera ejection fraction had a normal ejection fraction by nuclear stethoscope. Another subset of four patients had a normal ejection fraction by both gamma camera and nuclear stethoscope and abnormal regional wall motion on scintiangiography. In both subsets other nuclear stethoscope variables reflecting left ventricular systolic emptying rates, diastolic filling rates, diastolic timing intervals and relative cardiac output and volumes were able to predict abnormal ventricular performance as determined by gamma camera criteria despite a normal probe ejection fraction. This is not unexpected because it is reasonable that some patients with abnormal function will have significant alterations of systolic and diastolic flow rates and timing intervals in the presence of a normal ejection fraction.

TABLE I

Mean, Standard Deviation and Standard Error of the Mean Analysis of Individual Nuclear Stethoscope-Derived Variables in the Normal and Abnormal Groups

	EF	PEP	(%)*	LVET	(%)*	FFT	(%)*	$LVFT_2$	(%)*	EJR	FFR	EF/FFT	RCO	SV	EDV
Normal Group (Group Ia, normal wall motion; n = 18)															
Mean	76.7	0.11	18.5	0.29	36.3	0.243	30.5	0.181	20.4	4.42	4.74	330	95.2	1.25	1.63
SD	8.1	0.06	26.0	0.04	6.4	0.05	9.0	0.138	11.9	0.86	1.48	76.7	20.9	0.23	0.114
SEM	1.9	0.01	6.2	0.009	1.5	0.01	2.1	0.03	2.8	0.20	0.35	18.1	4.9	0.05	0.027
Abnormal Group (Group Ib, diffuse hypokinesia plus Group II, asynergy; n = 50)															
Mean	43.6	0.13	15.3	0.28	35.0	0.263	34.3	0.154	16.3	2.13	1.80	171	44.1	0.58	1.26
SD	15.6	0.06	7.0	0.05	6.85	0.06	10.3	0.156	11.5	0.94	0.89	64.8	18.7	0.24	0.228
SEM	2.2	0.008	0.99	0.007	0.96	0.008	1.4	0.02	1.6	0.13	0.13	9.1	2.6	0.03	0.032

* Indicates a rate-related division of the preceding individual variable by the total cardiac cycle time interval.
EDV = end-diastolic volume; EF = ejection fraction; EF/FFT = ejection fraction divided by fast filling time; EJR = ejection rate; FFR = fast filling rate; LVET = left ventricular ejection time; $LVFT_2$ = left ventricular diastasis time including atrial systole; RCO = relative cardiac output; SD = standard deviation; SEM = standard error of the mean.

TABLE II

Comparative Sensitivity, Specificity, Predictive Value and Risk Ratio Analysis for the Individual Functional Variables Derived From Probe Time-Activity Curves in Detecting Ventricular Function*

	$EF^{\dagger}$	EF	PEP	PEP%	LVET	LVET%	FFT	FFT%	$LVFT_2$	$LVFT_2$%	EJR	FFR	EF/FFT	RCO	SV	EDV	RCO EF/FFT FFR EJR‡
Sensitivity (%)	88	100	18	18	12	16	68	60	18	6	96	94	92	98	100	100	100
Specificity (%)	100	83	64	65	71	89	44	54	73	84	89	89	99	100	83	83	100
Predictive value (%)	100	94	82	90	67	80	77	67	69	60	96	96	96	100	94	94	100
Risk ratio	4	∞	1.1	1.3	0.9	1.1	1.2	0.9	0.9	0.8	4.8	6.2	4.8	19	∞	∞	∞

* An abnormal value was defined as a value below the mean normal value less standard deviation (66.8 percent confidence level). † 95 percent confidence level. ‡ Combined scoring system: the presence of any two of the three variables above or below the 66.8 percent confidence level represents normal or abnormal function, respectively.

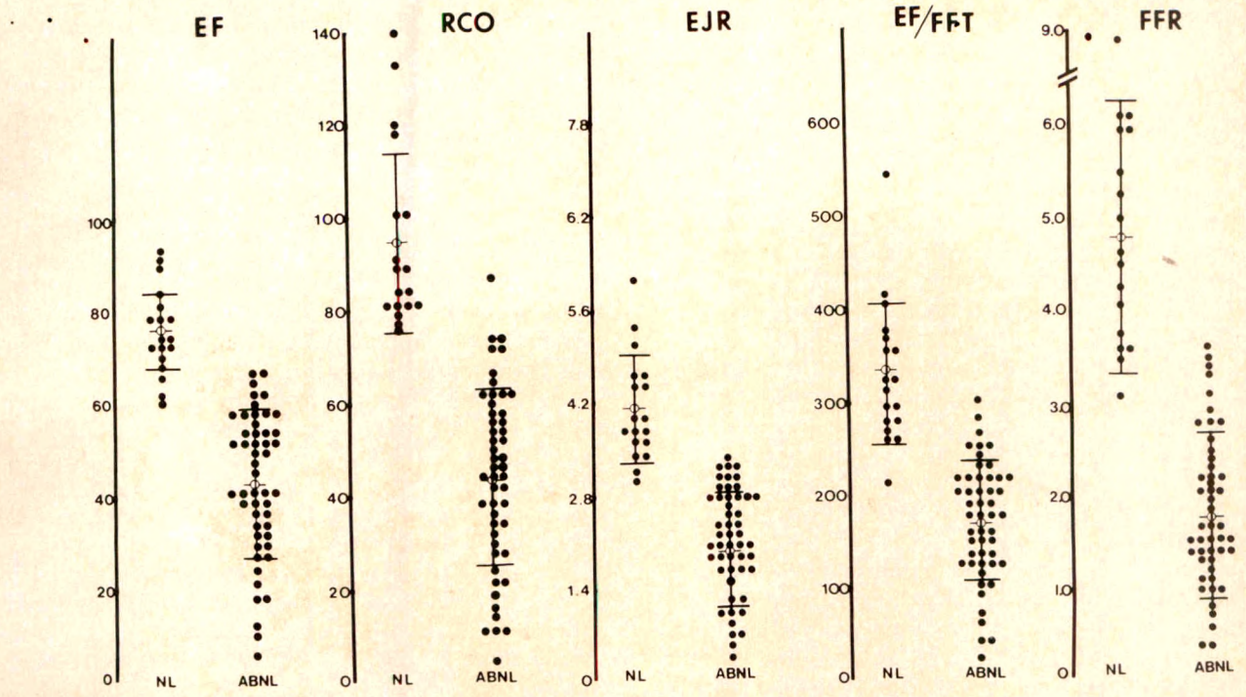

FIGURE 3. Distribution of selected left ventricular function variables derived from the nuclear stethoscope time-activity curves. Patients with a normal (NL) or abnormal (ABNL) left ventricle were so defined by conventional Anger camera scintiangiographic criteria. EF = ejection fraction; FFR = fast filling rate; EF/FFT = ejection fraction divided by the fast filling time; EJR = ejection rate; RCO = relative cardiac output. **Open circles** represent the mean and **bars** represent ±1 standard deviation.

Left ventricular ejection rate versus ejection fraction: Radioisotopic quantification of left ventricular ejection rate acquired by first pass imaging methods with a multicrystal camera-computer system[28] and by gamma camera gated equilibrium techniques[29] has proved as sensitive as radioisotopic ejection fraction analysis in detecting abnormal left ventricular performance. A significant reduction in fast filling rate was uniformly found in patients with angiographically validated coronary artery disease in the absence of hypertrophy or valve disease by Young et al.[30] using first pass multicrystal camera techniques. Significant rate-related prolongation of the fast filling time was shown by Qureshi et al.[18] in patients with hypertensive, ischemic or idiopathic cardiomyopathy with the gated equilibrium imaging technique. In our study, the crude systolic and diastolic timing intervals were as useful for detecting ventricular dysfunction as were the more complex rate-corrected timing interval analysis. However, no single probe-derived timing interval proved a better predictor of dysfunction than ejection fraction. There was a tendency of the fast filling time to prolong in the abnormal group relative to the ejection fraction-matched normal population. Nonetheless, the timing intervals may provide useful information in particular clinical settings or in characterizing a specific cardiomyopathy.

Relative cardiac versus output ejection fraction: The best single predictor of dysfunction, the relative cardiac output, is most problematic. This represents the double product of heart rate and relative stroke volume. A small group of patients with regional dyskinesia by Anger camera studies had depressed nuclear stethoscope-derived relative cardiac output and relative stroke volume, despite an ejection fraction that fell within the established normal range. Diminution in the relative cardiac output and relative stroke volume could represent the nuclear stethoscope impression of a "reduced" left ventricular volume by virtue of a noncontracting segment of the chamber identified and subtracted away mistakenly as background. This is further suggested by the significant overestimation by the nuclear stethoscope of ejection fraction in patients with regional wall motion abnormalities (Group II) compared with the ejection fraction in the combined group of patients with normal and global hypokinesia (Groups Ia and Ib).

Methodologic problems: The ejection fraction by nuclear techniques is derived by the standard formula:

Ejection fraction percent = End-diastolic counts − End-systolic counts × 100/End-diastolic counts − background counts

Systematic overestimation of background would produce an overestimation of global ejection fraction. Analysis of mean background determinations revealed such a significant increase in background in Group II when compared with values in Group Ia and Group Ib. This anomaly of the nuclear stethoscope data is also

presumably in part created by the positioning strategy, which tends to locate the probe field of view over the best contracting segment of the left ventricle, while excluding counts from poorly contracting segments and instead incorrectly adding these valid left ventricular counts to the background field of view. The relative cardiac output would thus prevent the overestimation of left ventricular function obtained in patients with regional asynergy with use of ejection fraction analysis alone because the background subtraction is weighted less in the relative cardiac output than in the ejection fraction analysis. This method of analysis produces a greater overestimation of ejection fraction than of relative cardiac output proportional to the extent of dyskinesia of the left ventricle. Comparison of ejection fraction with relative cardiac output ratios could potentially predict regional wall motion abnormalities (ischemic cardiomyopathy) with this nonimaging detector system.

Sensitivity, specificity and predictive value of method: The relative cardiac output, ejection rate, fast filling rate, and ejection fraction divided by the fast filling rate are the most accurate single nuclear stethoscope predictors of cardiac dysfunction. The sensitivity and specificity for the detection of dysfunction are expanded by considering these variables together. All patients with abnormal results on gamma camera analysis could be accurately selected out when two of any three of these variables were abnormally depressed (defined as 1 standard deviation less than the mean value derived from the normal population). All patients with normal gamma camera studies could be identified by normal values for two of any three of these variables.

Implications: These results suggest that radionuclide angiography with an electrocardiogram gated scintillation probe is a sensitive, rapid and potentially cost-effective portable method for screening for left ventricular dysfunction. The diagnostic yield from the nuclear stethoscope compares favorably with that from the more elaborate and costly gamma camera-computer system. Because stress testing in conjunction with imaging, contrast or radionuclide, increases the sensitivity for the detection of coronary artery disease, probe-monitored stress tests may provide an even more sensitive technique than the resting procedure described in this study. High temporal resolution time-activity curves recorded by this device provide numerous variables of left ventricular function that appear to be more sensitive and specific than ejection fraction analysis alone in a detection of abnormal ventricular performance. A large scale clinical trial is needed to determine the predictive value of probe-derived variables for defining the specific nature of cardiac dysfunction as well as the utility of probe-monitored stress tests.

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Method for Quantitative Analysis of Regional Left Ventricular Function With First Pass and Gated Blood Pool Scintigraphy

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The ability of radionuclide angiocardiography to quantitatively assess regional left ventricular function was studied in 33 patients undergoing biplane left ventricular cineangiography (45° right anterior oblique projection, and 60° left anterior oblique projection with 25° caudocranial angulation), and first pass (30° right anterior oblique projection) and multiple gated equilibrium (35° to 45° left anterior oblique projection with 20° to 25° caudocranial angulation) left ventricular scintigraphy within 48 hours. End-diastolic and end-systolic silhouettes of contrast angiograms were superimposed, and five segments were defined in each plane by radial lines originating from the end-diastolic center of mass. Segmental angiographic ejection fraction (end-diastolic area − end-systolic area/end-diastolic area) was calculated for each segment by computerized planimetry. Similar segments were defined in the end-diastolic and end-systolic regions of interest of the first pass and gated left ventricular scintigrams, and the segmental scintigraphic ejection fraction (background-corrected end-diastolic counts − background-corrected end-systolic counts/background-corrected end-diastolic counts) was obtained for each.

A good correlation was observed between segmental angiographic and scintigraphic ejection fraction in the segments corresponding to the anterobasal ($r = 0.74$), anterolateral ($r = 0.70$), apical ($r = 0.77$), diaphragmatic ($r = 0.71$), distal septal ($r = 0.66$), posterolateral ($r = 0.71$) and inferolateral ($r = 0.60$) left ventricular regions. The poor correlation in the posterobasal ($r = 0.39$), basal septal ($r = -0.02$) and superolateral ($r = 0.05$) segments was probably related to difficulty in defining the aortic valve, overlap of the left atrium and the left ventricle, and inability to visualize the high septum with these scintigraphic techniques. The reproducibility of scintigraphic segmental ejection fraction was studied in 13 patients in whom a second gated scintigram was performed 2 hours after the initial one. Excellent agreement ($r = 0.93$) was observed for scintigraphic segmental ejection fraction in the distal septal, posterolateral and inferolateral segments. Segmental scintigraphic ejection fraction enables accurate quantitative evaluation of the function of the anterobasal, anterolateral, apical, diaphragmatic, distal septal, posterolateral and inferolateral left ventricular regions with high reproducibility.

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Accurate analysis of regional left ventricular performance is of particular interest in patients with coronary artery disease, in whom neighboring areas of normal and abnormal left ventricular function are frequently present at rest or develop during exercise. Traditionally, contrast angiography has been employed to assess left ventricular function,[1–3] but more recently radionuclide angiocardiography has become available and has proved valuable in the evaluation of left ventricular function in these patients.[4–7] However, it has been shown that subjective analysis of left ventricular angiograms and scintigrams is characterized by a significant error rate and interobserver variability,[8–11] and objective analysis is essential for adequate definition and quantification of regional left ventricular function.

Several methods have been employed for objective evaluation of regional function with contrast left ventricular angiograms,[12–16] and some of these have been applied to the analysis of radionuclide angiocardiograms.[5,17–19] These angiographic methods, usually based on segmental changes in radii, hemiaxes or area, require precise identification of left ventricular margins, and are limited by the spatial resolution and edge definition of radionuclide studies. In addition, these methods ignore the three dimensional perspective provided by radioactive emission and thus limit the information to a single plane.

The purpose of this study was to develop a method that would enable accurate quantitative assessment of regional left ventricular function employing first pass and multiple gated radionuclide angiocardiography.

Methods

Patients

The study group consisted of 33 patients, 27 men and 6 women, undergoing diagnostic cardiac catheterization for suspected ischemic heart disease. The mean age of the patients was 53 years (range 37 to 73). In the postabsorptive state, approximately 60 minutes after premedication with atropine, 0.6 mg intramuscularly, and diphenhydramine (Benadryl®), 50 mg orally, all patients underwent right and left cardiac catheterization. Initial hemodynamic determinations were followed by biplane left ventricular cineangiography and selective coronary arteriography. Twenty-nine patients were found to have coronary artery disease (70 percent or greater reduction in luminal diameter of at least one major coronary artery), and 4 had no evidence of cardiac disease. Within 48 hours of contrast angiography, and during stable hemodynamic conditions, all patients underwent first pass and multiple gated equilibrium left ventricular scintigraphy. Patients receiving medications were maintained on the same dosage and no changes were made in the interval between angiographic and scintigraphic studies.

Angiographic Studies

Biplane left ventricular cineangiograms were performed in a 45° right anterior oblique projection and 60° left anterior oblique projection with 25° caudocranial ("axial") angulation. These projections, performed routinely at our institution, improve the evaluation of left ventricular wall motion without compromising left ventricular volume quantitation in comparison with data obtained from conventional 30° right anterior oblique and 60° left anterior oblique biplane cineangiography.[20] Filming was performed at 30 frames/s during power injection of 60 ml of sodium and meglumine diatrizoates (Renografin®-76) through an 8 French Cook pigtail catheter over a period of 3 seconds.

Data processing: Left ventricular volumes and ejection fraction were determined from biplane end-diastolic and end-systolic frames using area-length method.[21] Frames were selected by visual inspection, and films exposed during premature contractions or the following cycle were excluded from analysis. Regional left ventricular function was assessed angiographically by a method previously reported from our institution[22] that has been shown to define and quantitate regional left ventricular contraction accurately. Figures 1 and 2 illustrate this method in a patient with triple vessel coronary disease and severe left ventricular dysfunction. Consecutive end-diastolic and end-systolic frames were traced by trained technicians and superimposed using two external X-ray beam markers as a reference system. The ventricular silhouettes were then digitized with the stylus of a spark-gap x-y digitizing pen (Graf/Pen Science Accessories Corp., Southport, Connecticut) interfaced to an IBM 1800 computer system.[23]

In the right anterior oblique projection (*Fig. 1*), the center of mass of the end-diastolic silhouette (obtained as the average

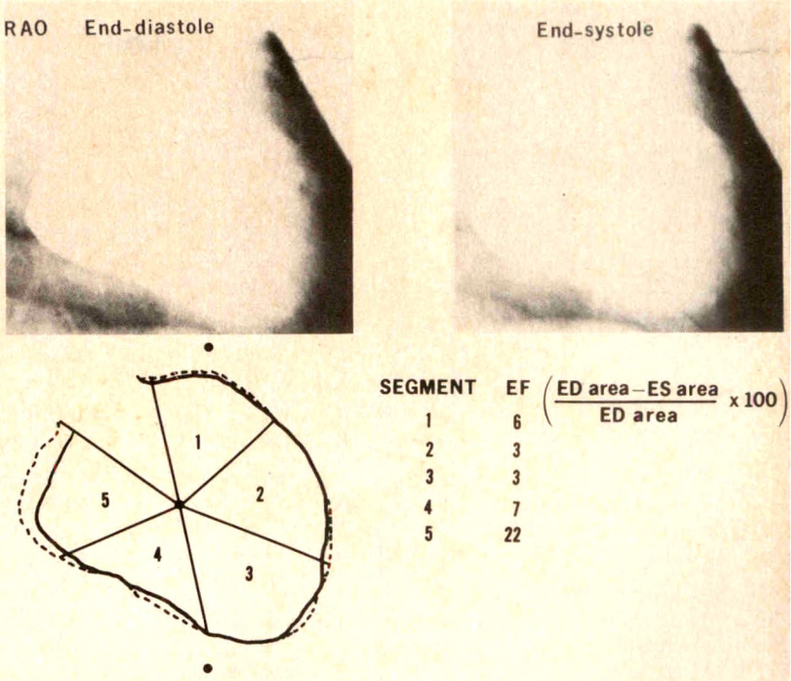


FIGURE 1. End-diastolic (ED) (**upper left**) and end-systolic (ES) (**upper right**) frames of a right anterior oblique (RAO) left ventriculogram in a patient with severe coronary artery disease and left ventricular dysfunction. In the **lower panel** (**left**), the end-diastolic (**dashed line**) and end-systolic (**solid line**) silhouettes have been superimposed using two external X-ray beam markers (**solid dots**). Five segments have been defined as described in the text, and segmental angiographic ejection fraction (EF) calculated for each (**right**).

x and y position of all discrete points within the silhouette[24]) was used as the vertex of the angle between the left margin of the aortic valve and the apex. This angle was divided into fifths. Segment 1 (anterobasal) comprised the first two fifths of the angle and segment 2 (anterolateral) the next two fifths. The angle between the right margin of the aortic valve and the apex was obtained similarly and also divided into fifths. Segment 5 (posterobasal) was the first two fifths of this angle, and segment 4 (diaphragmatic) was the next two fifths. Segment 3 (apical) was the remaining area from the left and right sides. In this manner, five segments were defined in the right anterior oblique projection.

In the axial left anterior oblique projection (*Fig. 2*), the center of mass of the end-diastolic left ventricular silhouette was also used to define the angle between the right margin of the aortic valve and apex. This angle was bisected, giving segments 6 (basal septal) and 7 (distal septal). The angle between the left margin of the aortic valve and apex was divided into three equal angles, segments 8 (posterolateral), 9 (inferolateral) and 10 (superolateral).

Segmental angiographic ejection fraction was calculated for each segment by computerized planimetry as follows: Segmental angiographic ejection fraction = [(segmental end-diastolic area − segmental end-systolic area)/segmental end-diastolic area)] ×100.

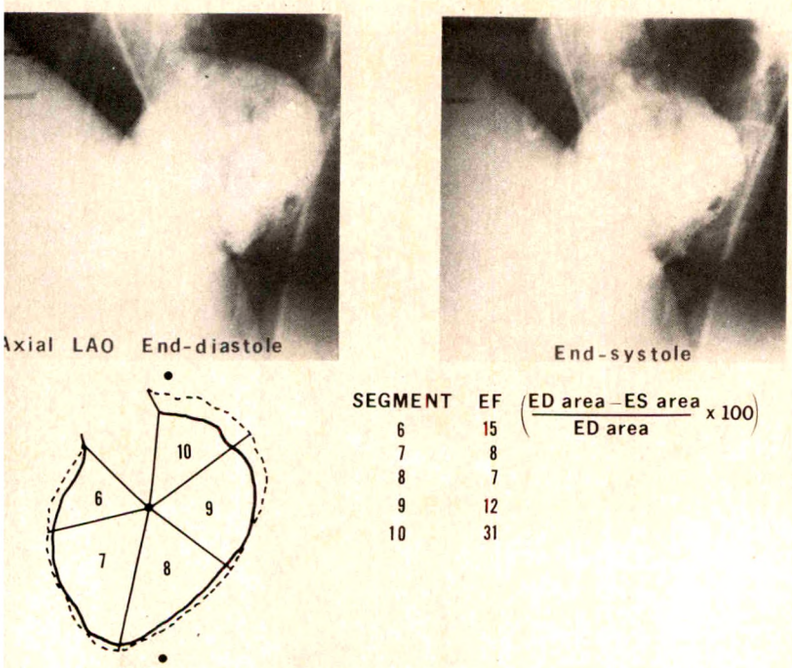
Radionuclide Studies

Within 48 hours of contrast angiography, and during stable and unchanged hemodynamic conditions, first pass and gated blood pool left ventricular angiocardiograms were obtained in all patients. The gamma camera was positioned in a 30° right anterior oblique projection for the first pass studies and in a 35° to 45° left anterior oblique projection with 20° to 25° of caudocranial angulation for the gated studies. Thus the right anterior oblique angiographic projection was similar to the first pass scintigraphic projection, and the axial left anterior oblique angiographic projection was similar to the gated scintigraphic projection.

Radionuclide studies were obtained using a mobile single crystal scintillation camera (Ohio Nuclear Series 120) equipped with digital magnetic tape and an all purpose parallel hole collimator. Red blood cells were labeled in vivo[25] by injecting 3 mg of stannous pyrophosphate (Pyrolite,® New England Nuclear) 30 minutes before the injection of 18 to 20 mCi of technetium-99m pertechnetate as a bolus dose into an antecubital vein, or into the right atrium in patients with a double lumen Swan-Ganz catheter positioned in the pulmonary artery. The first passage of activity was recorded on magnetic tape in list mode at a maximal rate of 30,000 counts/s. For 20 mCi and the particular collimator used, count rate saturation occurred only at the initial passage of the bolus injection into the right heart chambers.

Patients remained at bed rest after the first pass study, and after equilibration of the radionuclide in the vascular space (10 to 15 minutes), the gated blood pool study was performed. The data were stored on magnetic tape with the electrocardiographic signal stored as 1 pixel in a 256 by 256 matrix in a digitized frequency modulated format. In this use, the magnetic tape had a maximum count rate of 15,000 counts/s, but the practical maximum was approximately 11,000 counts/s to ensure that the electrocardiographic signal would not be subject to pulse pile-up effects. The tape unit had 6 minutes of recording time for a total of 3 to 3.5 million events for the complete study.

Data processing: Processing of the data was accomplished with an Informatek computer (Simis 3). For first pass studies, data were read and stored on the computer disk in list mode. Regions of interest were drawn over the superior vena cava, the right ventricle and the left ventricle. Time-activity curves for 1 second intervals were formed from each region of interest, and were used for quality control of the bolus of activity. The left ventricular time-activity curve was used to define the levophase for high frequency framing. Three to six beats were selected, and a composite cardiac cycle was formed consisting of 16 sequential frames (30 to 60 ms/frame). For processing of the gated blood pool studies, data were replayed through



SEGMENT	EF $\left(\frac{\text{ED area} - \text{ES area}}{\text{ED area}} \times 100\right)$
6	15
7	8
8	7
9	12
10	31

FIGURE 2. End-diastolic (ED) (**upper left**) and end-systolic (ES) (**upper right**) frames of an axial left anterior oblique (LAO) left ventriculogram in the same patient as in Figure 1. In the **lower panel** (**left**), end-diastolic (**dashed line**) and end-systolic (**solid line**) silhouettes have been superimposed using external X-ray beam markers (**solid dots**). Five segments have been defined as described in the text, and segmental angiographic ejection fraction (EF) calculated for each (**right**).

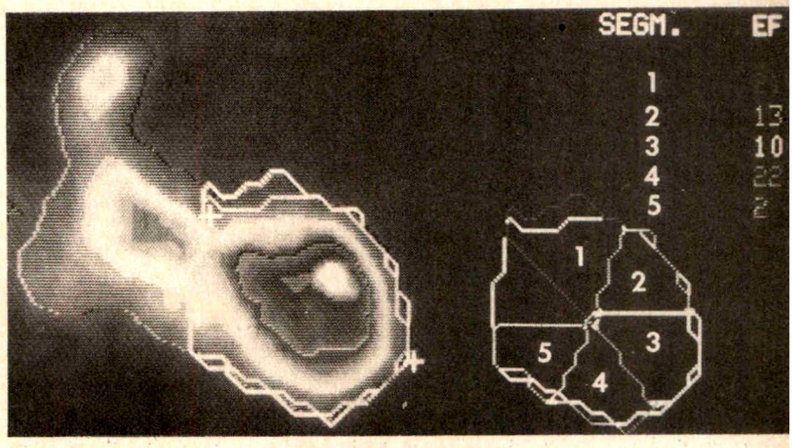


FIGURE 3. Superimposed end-diastolic left ventricular regions of interest of a right anterior oblique first pass scintigram in the same patient as in Figures 1 and 2. On the **right**, the regions of interest are divided into five segments (SEGM.) as described in the text, and the segmental scintigraphic ejection fraction (EF) is listed for each.

a magnetic tape unit interfaced to the computer. The electrocardiographic signal was reconstructed and used by the computer to gate the position data into 16 time intervals between R waves.

The first pass and gated equilibrium data were presented in a similar format, and the same program was used for processing each. The processing technique followed that of Pavel and co-workers[26,27] with modifications. After spatial smoothing, end-diastolic and end-systolic left ventricular regions of interest were formed by the isocount contours that best encompassed those images, and a valve plane was manually drawn to close each region of interest. As an aid for contour selection, edge-enhanced images were used in conjunction with the end-diastolic and end-systolic images. A computer-initiated background region of interest was formed around the apex and lateral wall of the left ventricle on the end-systolic image. Time-activity curves for the end-diastolic and end-systolic regions of interest were formed.

Left ventricular ejection fraction was calculated as follows:

$$\text{Ejection fraction} = [(ED_d - B_d) - (ES_s - B_s)/(ED_d - B_d)] \times 100,$$

where ED_d = end-diastolic counts from the end-diastolic time-activity curve; B_d = background normalized to the number of pixels in the end-diastolic region of interest; ES_s = end-systolic counts from the end-systolic time-activity curve; and B_s = background normalized to the number of pixels in the end-systolic region of interest.

The method employed for quantitative analysis of regional left ventricular function from first pass and multiple gated blood pool scintigrams is illustrated in Figures 3 and 4, for the same patient whose contrast left ventriculograms are shown in Figures 1 and 2. The superimposed end-diastolic and end-systolic regions of interest in the first pass (Fig. 3) and multiple gated blood pool (Fig. 4) scintigrams were divided in five segments by radial lines originating from the center of mass of the end-diastolic region of interest. For the first pass scintigrams, the segments were defined as in the right anterior oblique contrast angiograms, and for the gated blood pool scintigrams they were defined as in the axial left anterior oblique contrast angiograms. Thus each of the 10 angiographic segments had a corresponding scintigraphic segment that closely represented the same region of the left ventricle.

The ejection fraction for each scintigraphic segmet (segmental scintigraphic ejection fraction) was calculated as follows:

$$\text{Segmental scintigraphic ejection fraction} = [(\text{Segmental ED} - B_d) - (\text{segmental ES} - B_s)/(\text{segmental ED} - B_d)] \times 100,$$

where segmental ED = segmental end-diastolic counts, B_d = background normalized to the number of pixels in the segment at end-diastole, segmental ES = segmental end-systolic

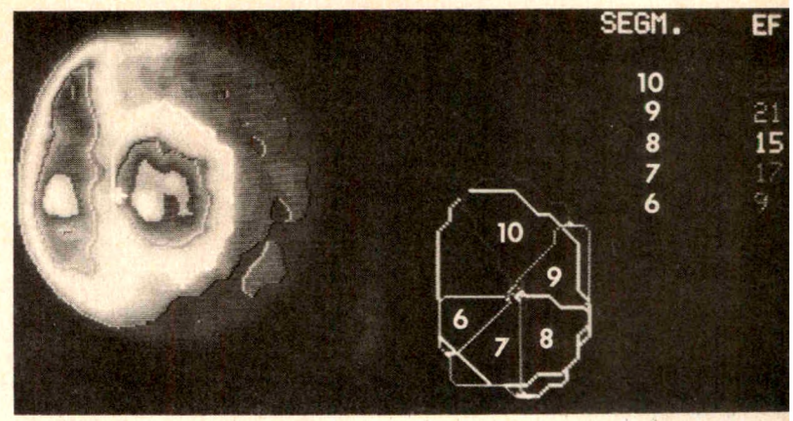


FIGURE 4. Superimposed end-diastolic and end-systolic left ventricular regions of interest of axial left anterior oblique gated scintigram in the same patient as in Figures 1 to 3. On the **right,** the regions of interest are divided into five segments (SEGM.) as described in the text, and the segmental scintigraphic ejection fraction (EF) is listed for each.

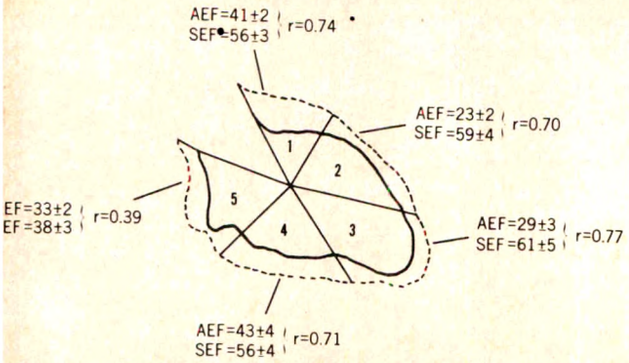


FIGURE 5. Correlation of the angiographic (AEF) and scintigraphic segmental ejection fractions (SEF) for right anterior oblique contrast ventriculograms and first pass scintigrams (mean ± standard error of the mean; n = 33). Values for segmental ejection fraction are shown as percent.

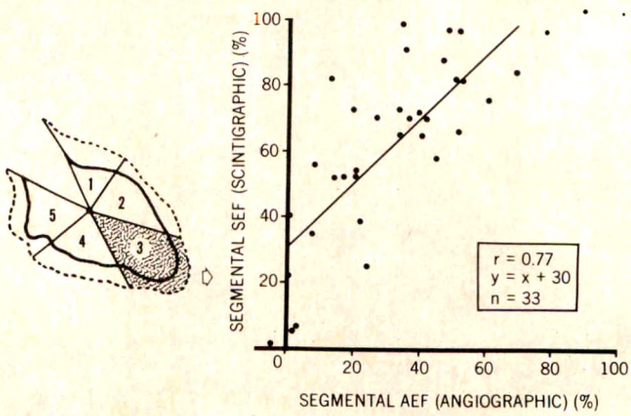


FIGURE 7. Correlation of the angiographic (AEF) and scintigraphic segmental ejection fractions (SEF) in apical segment 3.

counts, and B_s = background normalized to the number of pixels in the segment at end-systole.

Statistical analysis: Angiographic and scintigraphic ejection fractions are reported as mean percent ± standard error of the mean. Regression analysis was performed using the least squares method, and Student's paired *t* test was employed to assess the significance of differences between the observed linear regression analysis and the line of identity.

Results

Ejection fraction: Left ventricular ejection fraction obtained from biplane cineagiography (mean 45 percent, range 16 to 65) correlated well with ejection fraction calculated from first pass scintigraphy (r = 0.86, first pass ejection fraction = biplane angiographic ejection fraction + 5) and gated blood pool scintigraphy (r = 0.77, gated blood pool ejection fraction = 0.8 × biplane angiographic ejection fraction + 9).

Segmental ejection fraction: The correlation between segmental ejection fractions obtained from right anterior oblique contrast angiograms and first pass scintigrams in the 33 patients studied is depicted in Figure 5. A good correlation was found between angiographic ejection fraction and scintigraphic ejection fraction in the segments corresponding to the anterobasal (segment 1, r = 0.74), anterolateral (segment 2, r = 0.70), apical (segment 3, r = 0.77) and diaphragmatic (segment 4, r = 0.71) left ventricular regions. However, a very poor correlation was observed between angiographic and scintigraphic ejection fractions in the segment corresponding to the posterobasal left ventricular region (segment 5, r = 0.39). Figure 5 also shows that mean scintigraphic ejection fraction was considerably higher than the mean angiographic ejection fraction in segment 1 (56 ± 3 versus 41 ± 2 percent), segment 2 (59 ± 4 versus 23 ± 2 percent), segment 3 (61 ± 5 versus 29 ± 3 percent) and segment 4 (56 ± 4 versus 43 ± 4 percent).

The correlation between segmental ejection fractions obtained from axial left anterior oblique contrast angiograms and gated blood pool scintigrams is illustrated in Figure 6. A good correlation was present between angiographic and scintigraphic ejection fraction in the segments corresponding to the distal septal (segment 7, r = 0.66), posterolateral (segment 8, r = 0.71) and inferolateral (segment 9, r = 0.60) left ventricular regions. No correlation was found between the segments corresponding to the basal septal (segment 6, r = −0.02) and superolateral (segment 10, r = 0.05) regions. Mean scintigraphic ejection fraction was considerably higher than mean angiographic ejection fraction in all five segments: segment 6 (40 ± 3 versus 16 ± 5 percent), segment 7 (54 ± 4 versus 31 ± 3 percent), segment 8 (59 ± 5 versus 35 ± 5 percent), segment 9 (58 ± 4 versus 42 ± 3 percent) and segment 10 (46 ± 3 versus 30 ± 2 percent).

The best correlation between angiographic and scintigraphic ejection fractions was found in the apical region, corresponding to segment 3 in the right anterior oblique projection (Fig. 7). Although the correlation was good (r = 0.77), the linear regression line was significantly different ($p < 0.05$) from the line of identity, with scintigraphic ejection fraction equal to angiographic ejection fraction + 30, indicating consistently higher values for scintigraphic ejection fraction.

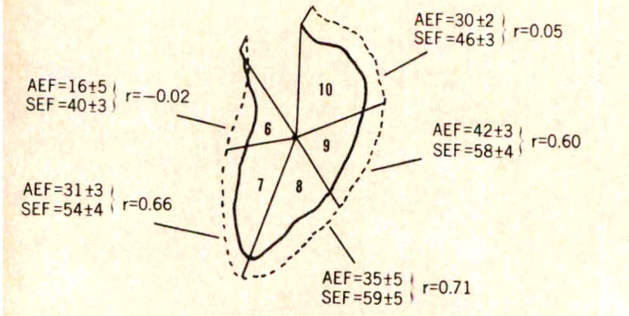


FIGURE 6. Correlation of the angiographic (AEF) and scintigraphic segmental ejection fractions (SEF) for axial left anterior oblique contrast ventriculograms and gated scintigrams (mean ± standard error of the mean; n = 33). Values for segmental ejection fraction are shown as percent.

Reproducibility of scintigraphic method: In order to assess the reproducibility of segmental scintigraphic ejection fraction, a second multiple gated left ventricular scintigram was performed in 13 randomly selected patients 2 hours after the initial study, with the gamma camera detector in the same axial left anterior oblique position. Since the segments corresponding to the basal septal (segment 6) and superolateral (segment 10) left ventricular regions correlated poorly with the corresponding angiographic segments, they were analyzed separately from the segments corresponding to the distal septal (segment 7), posterolateral (segment 8) and inferolateral (segment 9) regions. An excellent correlation ($r = 0.93$) was found between scintigraphic ejection fraction for segments 7, 8 and 9 on the first and second multiple gated studies, and the regression line (scintigraphic ejection fraction on second study = scintigraphic ejection fraction on first study + 5) did not differ significantly from the line of identity (intercept not different from 0, $p = 0.17$; slope not different from 1, $p = 0.30$). The reproducibility of segments 6 and 10 was considerably less, with $r = 0.63$ (scintigraphic ejection fraction on second study = 0.7 × scintigraphic ejection fraction on first study + 14).

To evaluate interobserver variability in the determination of segmental scintigraphic ejection fraction, 10 multiple gated left ventricular scintigrams were processed independently by two experienced operators. Interobserver variability was minimal, with excellent agreement between the two operators for segments 7, 8 and 9 ($r = 0.98$; scintigraphic ejection fraction by second operator = scintigraphic ejection fraction by first operator − 0.6). Interobserver variability was considerably greater for segments 6 and 10 ($r = 0.79$; scintigraphic ejection fraction by the second operator = 0.6 × scintigraphic ejection fraction by the first operator + 14).

Discussion

Regional left ventricular function in coronary artery disease: Regional left ventricular dysfunction is common in patients with coronary artery disease, and its extent and severity have important prognostic and therapeutic implications.[28–30] Recently, the development or worsening of regional left ventricular dysfunction during exercise has been shown to be a sensitive indicator of hemodynamically significant coronary stenoses.[4–7,31] However, subjective analysis of contrast and radionuclide left ventricular angiograms, is characterized by significant inter- and intraobserver variability,[8–11] and objective quantitative evaluation of regional ventricular function is essential in these patients. Techniques used to assess regional left ventricular function from contrast angiograms have been applied to the analysis of radionuclide angiograms.[5,17–19] These techniques, usually based on fractional changes in radii, hemiaxes or area, require reliable detection of left ventricular boundaries, often hampered by the miniature display and indistinct edges of radionuclide angiograms. In addition, scintigraphic studies provide recording of three dimensional radioactivity from the left ventricular cavity, information that is lost when bidimensional angiographic techniques are used to analyze regional left ventricular function from left ventricular scintigrams.

Quantitative assessment of regional left ventricular function: In the present study, we employed biplane axial left ventricular cineangiography (45° right anterior oblique and 60° left anterior oblique projection, 25° caudocranial angulation). These angiographic views are used routinely at our institution and have been shown to improve the evaluation of regional left ventricular wall motion without compromising left ventricular volume quantitation.[20] These angiographic projections, although not identical, were similar to the views employed in the first pass and gated left ventricular scintigrams. Previous work in our laboratory[22] has shown that segmental left ventricular wall motion can be accurately assessed from contrast cineangiograms by fractional changes in area of segments defined by radial lines originating from the center of mass of the end-diastolic left ventricular silhouette. In this study, we used the same method to divide the left ventricular regions of interest in the first pass and gated left ventricular scintigrams in five segments each. Therefore, it appeared reasonable to expect that corresponding angiographic and scintigraphic segments closely represented the same region of the left ventricle.

We found a good correlation between angiographic and scintigraphic segmental ejection fraction in the anterobasal, anterolateral, apical, diaphragmatic, distal septal, posterolateral and inferolateral left ventricular segments. Despite these good correlations, the mean values for segmental scintigraphic ejection fraction were consistently higher than the mean values for segmental angiographic ejection fraction (Fig. 5 to 7). Our method for quantitative analysis of regional left ventricular function by contrast angiography was based on changes in area as determined with planimetry and thus was only able to characterize wall motion in that portion of the left ventricular wall tangential to the X-ray beam. This method did not provide any information regarding the function of the neighboring myocardium that did not form a border with the X-ray beam. In contrast, segmental scintigraphic ejection fraction was derived from changes in end-diastolic and end-systolic counts in each segment, and thus should reflect segmental changes in blood volume influenced not only by the function of the border-forming portion of myocardial wall, but also by the function of nonborder-forming myocardium and probably by the function of neighboring segments. Although a myocardial depressant effect of sedatives and contrast medium during cardiac catheterization cannot be excluded as a factor in the lower values for segmental angiographic ejection fraction, the consistently higher values for segmental scintigraphic ejection fraction were expected as a reflection of changes in volume (cubic function) compared with changes in area (squared function). This represents a theoretical advantage of scintigraphy compared with angiography in the evaluation of regional left ventricular function.

The correlation between segmental angiographic and scintigraphic ejection fraction was very poor or nonexistent in segments 5, 6 and 10. This inadequate correlation, in addition to the rather poor reproducibility of these segments (6 and 10), was probably related to the difficulty in defining the mitral and aortic valve planes and high septum with radionuclide left ventricular angiocardiograms obtained in the right anterior oblique and axial left anterior oblique projections. Furthermore, any overlap between the left atrium and left ventricle in the axial left anterior oblique projection would affect end-diastolic and end-systolic counts in segment 10, but not necessarily the area of the corresponding angiographic segment. These observations are in agreement with those of other investigators[32] who have been unable to assess accurately the performance of the basilar left ventricular regions with gated blood pool scintigraphy in the left anterior oblique view.

Quantitative assessment of global left ventricular function: We also found a good correlation between global angiographic and scintigraphic left ventricular ejection fraction in the 33 patients studied. The correlation was better for first pass ($r = 0.86$) than for gated blood pool ($r = 0.77$) scintigraphy, and this may also be partly related to overlap between the upper and posterior portion of the left ventricle and left atrium in the axial left anterior oblique projection, so that this nonventricular source of radioactivity reaching the detector could result in greater error in the calculation of ejection fraction than that of studies performed in the right anterior oblique projection. In addition, background radioactivity is proportionately greater in gated than in first pass studies, and a small error in estimation of background would result in a proportionately greater error in the calculated ejection fraction.

Clinical implications: This study demonstrates that determination of segmental scintigraphic ejection fraction obtained from first pass and multiple gated blood pool left ventricular scintigrams performed in the right anterior oblique and axial left anterior oblique projections enables quantitative evaluation of the function of the anterobasal, anterolateral, apical, diaphragmatic, distal septal, posterolateral and inferolateral left ventricular regions with high reproducibility and minimal interobserver variability. Segmental scintigraphic ejection fraction can easily be obtained from radionuclide angiocardiograms and may be useful in precisely detecting and quantitating resting or exercise-induced regional left ventricular dysfunction, and thus aid in the noninvasive diagnosis of coronary disease. Additionally, it may prove useful in quantitating infarct size, monitoring the natural history of these patients, and evaluating changes resulting from physiologic, pharmacologic, metabolic and surgical interventions.

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Intravenous Xenon-133 for the Determination of Radionuclide First Pass Right Ventricular Ejection Fraction

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The use of intravenous xenon-133 for determination of radionuclide first pass right ventricular ejection fraction is described. First pass determinations of right ventricular ejection fraction were made with both xenon-133 and technetium-99m in 13 subjects (15 right ventricular ejection fraction determinations); results obtained with xenon-133 show an excellent correlation ($r = 0.98$, $p < 0.002$) with results obtained using technetium-99m. Because of rapid pulmonary elimination of xenon-133 from the body, the use of this radioisotope allows multiple first pass right ventricular ejection fraction determinations within a short period of time, without significant radiation exposure for the patient.

Radionuclide techniques have found widespread clinical application in recent years in the noninvasive assessment of left and right ventricular function. The radionuclide ejection fraction of the left ventricle can be measured by either the first pass or gated equilibrium method and correlates well with contrast angiographic methods.[1] Radionuclide right ventricular ejection fraction has been determined generally by the first pass technique, using a radiopharmaceutical containing technetium-99m.[2,3] Poor delineation of right ventricular borders has made quantitation of the right ventricular ejection fraction by the gated equilibrium method difficult, although two techniques employing the gated equilibrium method were recently reported.[4,5]

So that the patient will not be exposed to an excessive dose of radiation, a total of no more than 20 to 25 mCi of technetium-99m is administered during a radionuclide study, limiting the number of first pass radiopharmaceutical injections to two or less. The accumulation of background activity after two bolus injections of technetium-99m, which markedly affects the accuracy of any subsequent first pass ejection fraction determinations, also precludes more than two first pass injections on a given day. These considerations limit the usefulness of technetium-99m in determining first pass right ventricular ejection fraction in critical care situations where frequent, repeated studies are required.

We describe the use of intravenous xenon-133 with the first pass technique for right ventricular ejection fraction determination. Because the isotope is eliminated from the body rapidly through the lungs, the radiation dose is negligible compared with that associated with technetium-99m,[6] and background activity does not accumulate with successive injections; thus, multiple bolus injections of the isotope can be made, allowing serial studies of right ventricular ejection fraction within a short period with no additional radiation exposure for the patient.

Methods

Study subjects: Thirteen subjects were studied (Table I). Three were normal volunteers, and the remaining 10 were patients with the following clinical

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diagnoses: coronary artery disease with angina pectoris (4 patients), acute myocardial infarction, predominantly right ventricular (1 patient), congestive heart failure (3 patients), pulmonary hypertension (1 patient) and chronic obstructive pulmonary disease with cor pulmonale (1 patient).

Radionuclide imaging: Fifteen to 20 mCi of xenon-133 dissolved in 2 cc of saline solution, supplied in Carpules® (Mallinckrodt, Inc., St. Louis, Missouri), was transferred into a 3 cc glass syringe using a Carpule aspirator (Cook-Waite Laboratories, Inc., New York, New York); the Carpules contained 25 mCi of xenon-133 at the time of shipment, before radioactive decay. The contents of the syringe were injected rapidly as a bolus dose through a large antecubital vein using an indwelling Teflon® catheter (except in the patient with acute right ventricular infarction, in whom the radioisotope was injected directly into the right atrium through the proximal lumen of an indwelling Swan-Ganz thermodilution catheter). The bolus injection was followed with a 10 cc saline flush. Exhaled xenon was collected in a commercially available, mobile charcoal trap to assure that no xenon would escape into the environment and contaminate personnel.

The first transit of the radioactive bolus dose through the central circulation was recorded in the 30° right anterior oblique projection. For 10 of the 13 patients, a single crystal Anger gamma scintillation camera (Searle LFOV) equipped with a general purpose low energy parallel hole collimator was used, and data were acquired in list mode by a digital computer (NOVA computer, with MDS system). For the remaining three patients, a single crystal Anger gamma scintillation camera equipped with a high sensitivity low energy parallel hole collimator was used, and data were acquired in frame mode, 33 frames/s, by a digital on-board computer (Ohio Nuclear Sigma 420 with a VIP 550 on-board computer). For xenon-133 injections the gamma scintillation camera was set at a photopeak of 80 keV with a 20 percent window.

Calculation of right ventricular ejection fraction: The imaged data were replayed and a region of interest was assigned to the right ventricular blood pool, with the right atrium and pulmonary artery excluded from this region of interest, according to the method of Tobinick et al.[3] A second region of interest was assigned to noncardiac background structures. Time-activity curves were then generated from both the right ventricular and background regions of interest. Generally, peak right ventricular count rates ranged from 100 to 600 counts; these count rates corresponded to 33 ms time intervals when the Ohio Nuclear Sigma 420 camera with VIP computer was used, and 60 to 80 ms intervals when the Searle LFOV camera was used, depending on the heart rate. Background activity was minimal in comparison, with the average count rate 5 to 20 counts per time interval. After correcting the right ventricular time-activity curve for background ac-

TABLE I
Right Ventricular Ejection Fraction (RVEF) Values Obtained With Technetium-99m and Xenon-133 Techniques

Clinical Diagnosis	RVEF ^{99m}Tc	RVEF ^{133}Xe
Normal volunteer	0.41	0.41
Normal volunteer	0.47	0.51
Normal volunteer	0.36	0.38
CAD, angina	0.58	0.60
CAD, angina	0.47	0.53
CAD, angina	0.44	0.48
CAD, angina	0.45	0.44
AMI, predominantly RV		
Initial	0.13	0.13
3 weeks later	0.12	0.13
Congestive heart failure	0.53	0.50
Congestive heart failure	0.22	0.17
Congestive heart failure	0.54	0.56
Pulmonary hypertension	0.34	0.36
COPD with cor pulmonale		
Before isoproterenol	0.39	0.45
After isoproterenol	0.38	0.43

AMI = acute myocardial infarction; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; RV = right ventricular; ^{99m}Tc = values determined with technetium-99m technique; ^{133}Xe = values determined with xenon-133 technique.

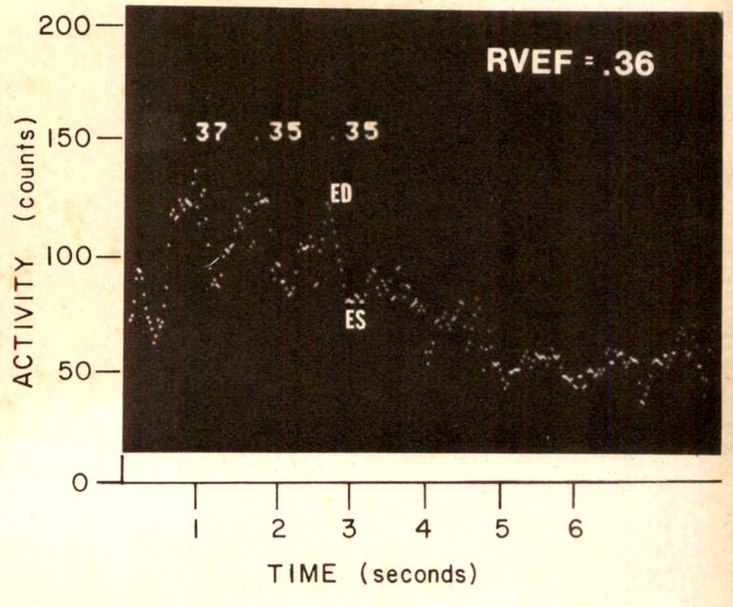

FIGURE 1. Background-corrected right ventricular time-activity curve using xenon-133. Each point represents the activity during a 33 ms interval (33 curve points/s). Right ventricular ejection fraction (RVEF) is calculated by dividing the difference in counts between end-diastole (ED) and end-systole (ES) by the number of counts at end-diastole for each beat. The average right ventricular ejection fraction for the three analyzed beats is 0.36.

tivity by subtracting the background time-activity curve, ejection fraction was calculated by dividing the difference in counts between end-diastole and end-systole (a value proportional to the stroke volume) by the number of counts at end-diastole (a value proportional to the end-diastolic volume). Only beats from the early downslope of the right ventricular time-activity curve were used for calculation. In general, two or three cardiac cycles were used for determining the ejection fraction and the values from the analyzed beats were averaged (Fig. 1).

Comparison with technetium-99m: In order to compare the new method with standard techniques, the same procedure was repeated using 10 to 15 mCi of technetium-99m–labeled human serum albumin instead of xenon-133 10 minutes after the xenon-133 injection. The 30° right anterior oblique projection was again utilized; the gamma scintillation camera used for the preceding xenon-133 injection in a particular patient was used for the corresponding technetium-99m injection, and the camera was set at a photopeak of 140 keV with a 20 percent window. Right ventricular ejection fraction was calculated in an identical fashion. In the patient with chronic obstructive pulmonary disease, injections of both radioisotopes were repeated after the sublingual administration of isoproterenol; in the patient with acute right ventricular infarction, studies were repeated 3 weeks after the initial studies. Thus right ventricular ejection fraction was determined 15 times in 13 subjects using each radioisotope.

Results

The radionuclide first pass right ventricular ejection fraction values determined with the technetium-99m and xenon-133 techniques for each of the 13 subjects studied are shown in Table I. In Figure 2, right ventricular ejection fraction determined with xenon-133 is plotted against right ventricular ejection fraction determined with technetium-99m for the 15 right ventricular ejection fraction determinations. The correlation coefficient is r = 0.98 ($p < 0.002$).

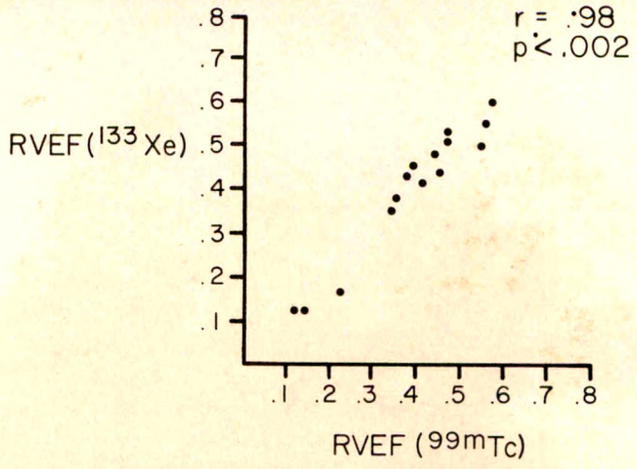

FIGURE 2. Right ventricular ejection fraction (RVEF) by the xenon-133 technique versus that by the technetium-99m technique.

Discussion

Right ventricular ejection fraction: clinical role: First pass radionuclide determination of right ventricular ejection fraction using technetium-99m has been employed to study right ventricular function in normal subjects and in patients with chronic obstructive pulmonary disease, pulmonary hypertension secondary to mitral or aortic valve disease, acute myocardial infarction and angiographically documented coronary artery disease.[2,3,7–12] Right ventricular ejection fraction is usually abnormal in patients with cor pulmonale secondary to chronic obstructive pulmonary disease, but it varies widely and may be normal in patients with chronic obstructive pulmonary disease without evidence of corpulmonale.[7,8] Impaired right ventricular ejection fraction is usually restored to normal after surgical relief of pulmonary hypertension in patients with mitral or aortic valve disease.[9] First pass determination of right ventricular ejection fraction has been useful in the identification of patients with inferior wall myocardial infarction who have associated right ventricular infarction.[3,9,10] Exercise studies in patients with angiographically documented coronary artery disease have yielded conflicting results: Johnson et al.[11] found that stenotic lesions of the proximal right coronary artery are associated with no change in the first pass right ventricular ejection fraction during exercise, whereas coronary artery disease not involving the proximal right coronary artery is associated with an increase in right ventricular ejection fraction during exercise. In contrast, Berger et al.[12] reported that the major determinant of the right ventricular ejection fraction response to exercise in patients with coronary artery disease is the concomitant left ventricular ejection fraction response to exercise, rather than the presence or absence of stenosis of the proximal right coronary artery.

Limitations of gated equilibrium techniques using technetium-99m: Two gated equilibrium techniques for right ventricular ejection fraction were described recently, one employing separate end-diastolic and end-systolic regions of interest[4] and the other using a single fixed end-diastolic region of interest[5]; both methods involve the use of technetium-99m. Although these techniques offer the possibility of serial measurement of right ventricular ejection fraction within a short period of time, they have potential limitations. In patients with severe right ventricular failure and marked right atrial enlargement, overlap between the right ventricle and right atrium will be seen in the left anterior oblique view even at end-systole, precluding clear separation of these structures when the right ventricular region of interest is assigned.[4] Difficulty in separating the pulmonary outflow tract from the body of the right ventricle can also be encountered in gated equilibrium determination of right ventricular ejection fraction.[5] Inability to exclude the right atrium and pulmonary outflow tract when assigning the right ventricular region of interest tends to make the gated equilibrium right ventricular ejection fraction lower than that determined by first pass studies.[5] Another disadvantage of the gated equilibrium techniques for right ventricular ejection fraction compared with first

pass studies is that at least 2 minutes of imaging time is required for the former, whereas the latter requires 30 seconds or less; this difference in data collection time can be important when acutely ill patients are studied or when interventions involving rapidly changing states are evaluated.

Xenon-133 for determination of radionuclide right ventricular ejection fraction: Xenon-133 is a chemically inert gas. It is produced by fission of uranium-235 and decays to cesium-133 with emission of gamma rays of 81 keV (33 percent). Xenon-133 has a physical half-life of 5.3 days and a biologic half-life of 1 to 2 minutes, the latter due to almost complete elimination of the radioisotope from the body in one passage through the lungs.[13] Only 5 percent of an injected intravenous dose of xenon-133 reaches the systemic circulation.[14]

By inhalation and intravenous injection, xenon-133 has been used in pulmonary ventilation studies.[15–17] Dissolved in saline solution and injected intraarterially, the radioisotope has been employed in the study of myocardial blood flow.[14,18] With constant infusion into the left ventricle, the use of xenon-133 for the quantitation of mitral regurgitation has been described.[19] In the present study, the use of intravenous xenon-133 for determination of first pass radionuclide right ventricular ejection fraction is described for the first time. Right ventricular ejection fraction determinations using xenon-133 showed an excellent correlation ($r = 0.98$, $p < 0.002$) with the results obtained using technetium-99m.

Advantages of xenon-133 technique: The advantages of using xenon-133 rather than technetium-99m in first pass determination of right ventricular ejection fraction are related to the rapid pulmonary elimination of the radioisotope: (1) The patient is exposed to a much lower radiation dose (less than 1/100 the radiation dose for a first pass bolus dose using technetium-99m,[6] and (2) background activity does not accumulate with successive bolus injections, as it does with technetium-99m. These factors allow multiple bolus injections and thus multiple first pass determinations of right ventricular ejection fraction in a patient within a short period. This feature is important in the critical care setting, where serial measurements of right ventricular ejection fraction involving extremely short imaging times can be made using xenon-133 before and after various interventions, and can provide potentially valuable information. One promising application of the xenon-133 technique for first pass right ventricular ejection fraction is in patients with acute myocardial infarction, predominantly right ventricular, complicated by cardiogenic shock: Serial first pass studies of right ventricular ejection fraction can supplement hemodynamic data in following the response to various therapeutic interventions such as administration of inotropic agents or intraaortic balloon pump counterpulsation.

Disadvantages of xenon-133 technique: The main disadvantage of xenon-133 at present is its cost. Because of little demand for its use, the amount of radioisotope necessary for one first pass injection costs approximately 16 times as much as an equivalent amount of technetium-99m. The rapid pulmonary elimination of xenon-133 is a second disadvantage: The lack of appearance of the radioisotope in significant concentration in the left ventricle in patients without a right to left shunt precludes determination of the left ventricular ejection fraction from the same first pass bolus injection.

In conclusion, the use of intravenous xenon-133 for measurement of radionuclide first pass right ventricular ejection fraction provides results that show an excellent correlation with values obtained using technetium-99m and offers the possibility of performing multiple first pass tests in a patient with no significant increase in radiation exposure.

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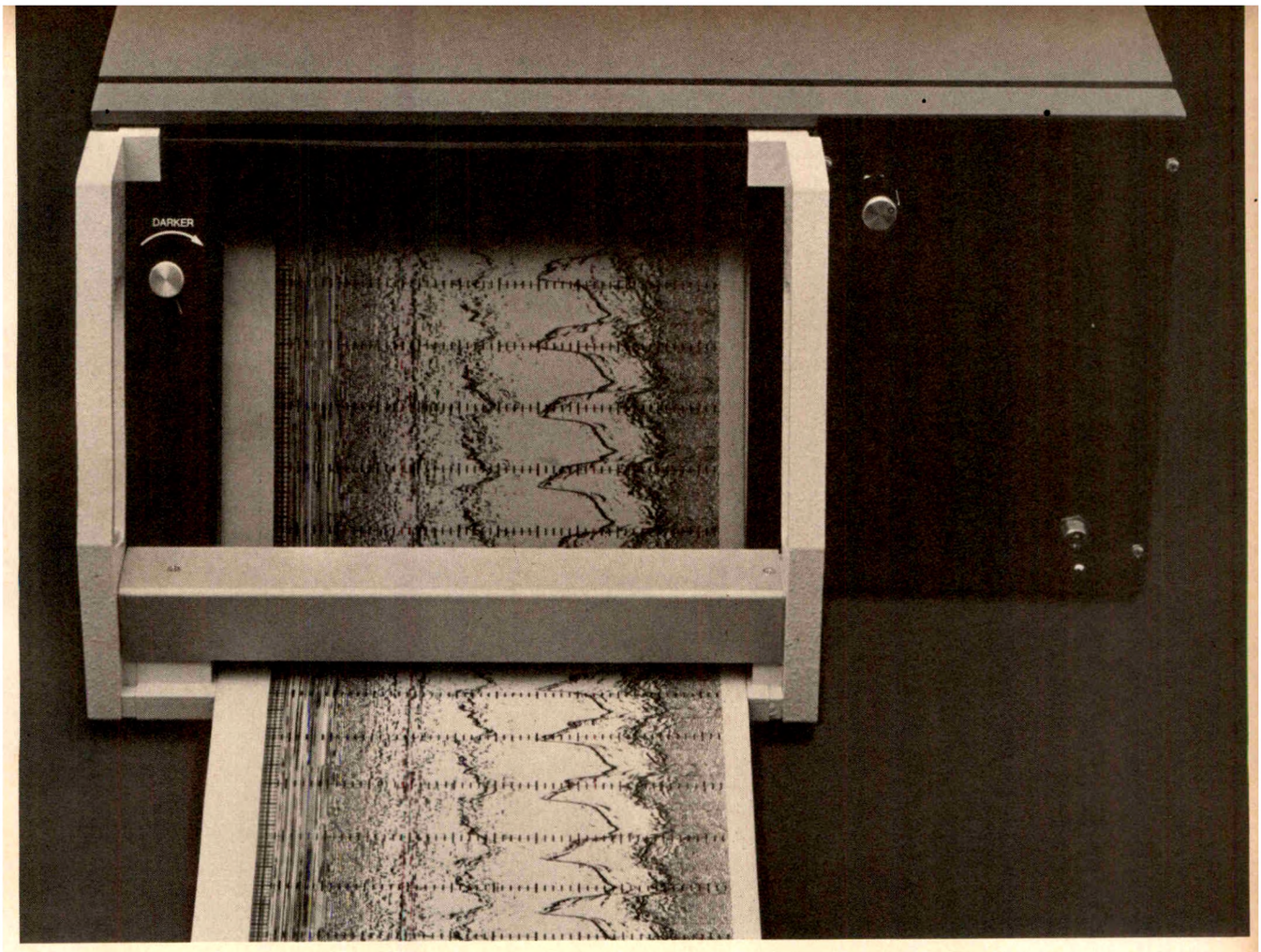

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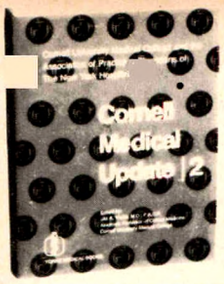

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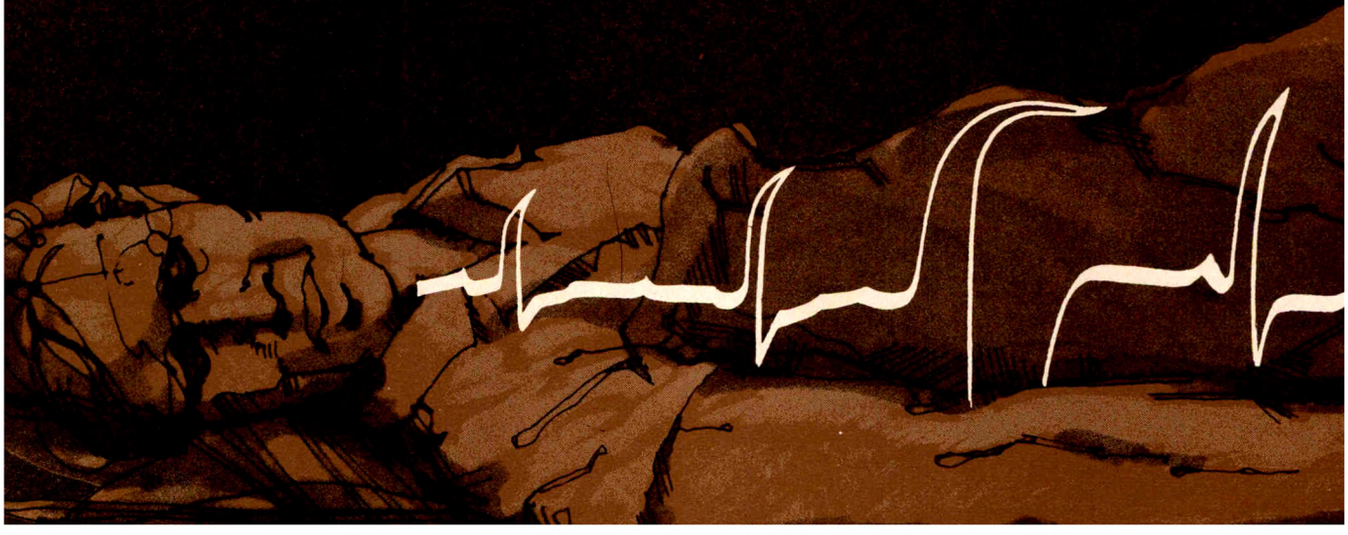

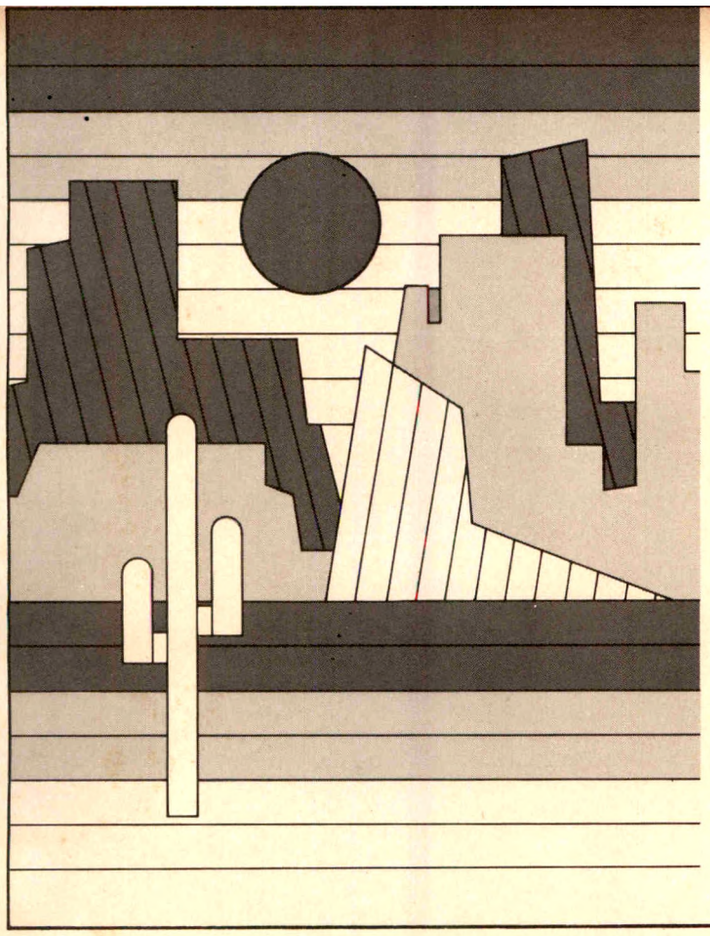

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The precautions to be observed include all those applicable to quinidine. A preliminary test dose of a single tablet of quinidine sulfate should be administered to determine if the patient has an idiosyncrasy to quinidine. Hypersensitivity to quinidine, although rare, should constantly be considered, especially during the first weeks of therapy.

Quinidine in large doses may reduce the contractile force of the heart, therefore, extreme caution should be exercised in using the drug in patients with severe heart disease, hypotension or digitalis intoxication. The potential disadvantages and benefits must be weighed.

It should be administered cautiously, if at all, to senile patients.

Hospitalization for close clinical observation, electrocardiographic monitoring, and possibly plasma quinidine levels is indicated when large doses are used or with patients who present an increased risk.

ADVERSE REACTIONS:
Symptoms of cinchonism, ringing in ears, headache, nausea, disturbed vision may appear in sensitive patients after a single dose of the drug.

Cardiovascular: Widening of QRS complex, cardiac asystole, ventricular ectopic beats, idioventricular rhythms including ventricular tachycardia and fibrillation, paradoxical tachycardia, arterial embolism, hypotension.

Gastrointestinal: Nausea, vomiting, abdominal pain, diarrhea.

Hematologic: Acute hemolytic anemia, hypoprothrombinemia, thrombocytopenic purpura, agranulocytosis.

Central Nervous System: Headache, fever, vertigo, apprehension, excitement, confusion, delirium and syncope, disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, reduced vision fields, photophobia, diplopia, night blindness, scotomata), optic neuritis.

Dermatologic: Cutaneous flushing with intense pruritus.

Hypersensitivity Reactions: Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest.

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THE PRE-EXCITATION SYNDROME: FACTS AND THEORIES

Libi Sherf, MD, FACC
Assoc. Professor of Cardiology, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine, and Visiting Assoc. Professor, Dept. of Medicine, University of Alabama.

Henry N. Neufeld, MD, FACC
Professor of Medicine and Chaim Sheba Professor of Cardiology, Chief, Heart Institute, Chaim Sheba Medical Center, Tel Hashomer, University of Tel Aviv—Sackler School of Medicine.

Every cardiologist, internist, pediatrician, surgeon—indeed, *every physician*—should have a good basic knowledge of the Pre-excitation Syndrome. Here are just a few reasons why this is so essential:

- ☐ ⅓ of all pre-excitation cases are misdiagnosed.
- ☐ 5% to 10% of all tachycardias in adults are produced by pre-excitation.
- ☐ In ½ of all infants under 10 months of age with life-threatening tachycardias, the tachycardias are actually secondary to pre-excitation.
- ☐ ⅓ to ½ of all children with pre-excitation have an additional heart disease.

Starting with Wolff, Parkinson and White's classic paper, this book gives a comprehensive summary of all important facts of pre-excitation, plus the authors' personal experiences of follow-up studies of patients through many decades. It also brings a broad view of the literature and discusses the different structural and physiological aspects which form the pathomechanism of pre-excitation.

"What is offered richly in this book is a methodical and comprehensive analysis of virtually all currently available knowledge on the subject. This is done with an admirable even-handedness, dealing objectively with all viewpoints but at the same time evaluating relative strengths and weaknesses of each observation and hypothesis. There is brought a wisdom here which only time and experience can provide. The encyclopedic references alone would make the book invaluable to anyone seriously interested in the Wolff-Parkinson-White syndrome. But when knowledgeable discussion and personal observations are added, it is genuinely a monumental contribution to clinical cardiology and cardiac electrophysiology."

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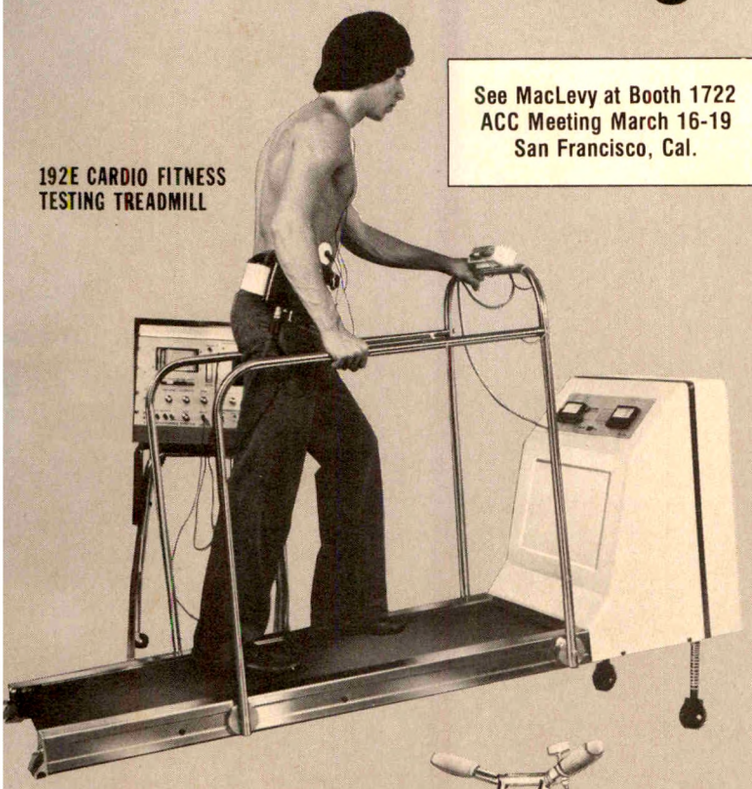

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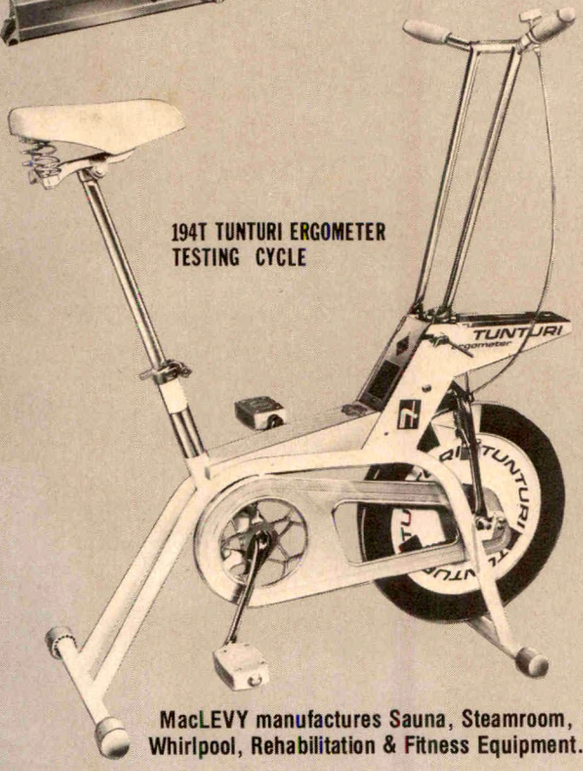

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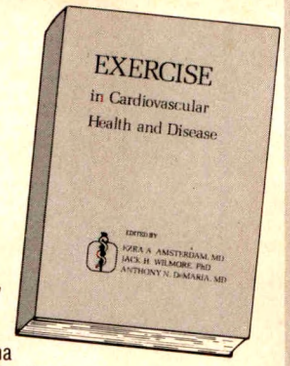

Edited by
Ezra A. Amsterdam, MD, Chief Coronary Care Unit, Univ. of Calif. School of Medicine
Jack H. Wilmore, PhD, Professor and Head Dept. of Physical Education & Athletics, Univ. Arizona
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Brief Summary of Prescribing Information

Indications Lopressor is indicated in the management of hypertension. It may be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.

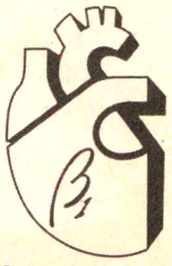
Contraindications Lopressor is contraindicated in sinus bradycardia, heart block greater than first degree, cardiogenic shock, and overt cardiac failure (see **Warnings**).

Warnings ***Cardiac Failure:*** Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and beta blockade carries the potential hazard of further depressing myocardial contractility and precipitating more severe failure. In hypertensive patients who have congestive heart failure controlled by digitalis and diuretics, Lopressor should be administered cautiously. Both digitalis and metoprolol slow AV conduction.

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or be given a diuretic, and the response observed closely. If cardiac failure continues, despite adequate digitalization and diuretic, Lopressor therapy should be withdrawn.

Ischemic Heart Disease: Following abrupt cessation of therapy with certain beta-blocking agents, exacerbations of angina pectoris and, in some cases, myocardial infarction have been reported. Even in the absence of overt angina pectoris, when discontinuing therapy, Lopressor should not be withdrawn abruptly, and patients should be cautioned against interruption of therapy without the physician's advice.

Bronchospastic Diseases: **PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. Because of its relative beta$_1$ selectivity, however, Lopressor may be used with caution in patients with bronchospastic disease who do not respond to, or cannot tolerate, other antihypertensive treatment. Since beta$_1$ selectivity is not absolute, a beta$_2$-stimulating agent should be administered concomitantly and the lowest possible dose of metoprolol should be used. It may be prudent initially to administer metoprolol in smaller doses three times daily, instead of larger doses two times daily, to avoid the higher plasma levels associated with the longer dosing interval. (See Dosage and Administration.)**



Still the most significant clinical advance in beta-blocker antihypertensive therapy

Major Surgery: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

Metoprolol, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported with beta blockers.

Diabetes Mellitus: Beta-adrenergic blockade may mask symptoms of hypoglycemia (e.g., tachycardia) and may potentiate insulin-induced hypoglycemia. Lopressor should therefore be used with caution in diabetic patients, especially those with labile diabetes.

Thyrotoxicosis: Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta blockade which might precipitate a thyroid storm.

Precautions ***Impaired Hepatic or Renal Function:*** The drug should be used with caution in patients with impaired hepatic or renal function.

Drug Interactions: Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. Patients treated with Lopressor plus a catecholamine depletor should therefore be closely observed for evidence of hypotension and/or marked bradycardia which may produce vertigo, syncope, or postural hypotension.

Long-Term Animal Studies: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In a one-year study in dogs, there was no evidence of drug-induced toxicity at or below oral doses of 105 mg/kg per day. Two-year studies in rats at three oral dosage levels of up to 800 mg/kg per day did not indicate an increase in the development of spontaneously occurring benign or malignant neoplasms of any type. The only histologic changes which appeared to be drug-related were an increased incidence of generally mild focal accumulation of foamy macrophages in pulmonary alveoli and a slight increase in biliary hyperplasia. Neither finding represents symptoms of a known disease entity in man. In a 21-month study in mice at three oral dose levels of up to 750 mg/kg per day, benign lung tumors (small adenomas) occurred more frequently in female mice receiving the highest dose than in untreated control animals. There was no increase in malignant lung tumors or total (benign plus malignant) lung tumors. The overall incidence of tumors or malignant tumors was also unaffected by metoprolol administration.

Usage in Pregnancy: Reproduction studies in animals did not reveal any evidence of impaired fertility or of teratogenic potential. There was evidence in the rat of increased postimplantation loss and decreased neonatal survival (threshold between 50 and 500 mg/kg). Distribution studies in mice confirm exposure of the fetus when metoprolol is administered to the pregnant animal. There are no well-controlled studies in pregnant women. Lopressor should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Since most drugs are excreted in human milk, nursing should not be undertaken by mothers receiving metoprolol.

Usage in Children: Safety and effectiveness in children have not been established.

Adverse Reactions Most adverse effects have been mild and transient.

Central Nervous System: Tiredness and dizziness have occurred in about 10 of 100 patients. Depression was reported in about 5 of 100 patients. Headache, nightmares, and insomnia have also been reported but drug relationship is not clear.

Cardiovascular: Shortness of breath and bradycardia have occurred in approximately 3 of 100 patients. Cold extremities; arterial insufficiency usually of the Raynaud type; palpitations and congestive heart failure have been reported. See **Contraindications, Warnings,** and **Precautions.**

Respiratory: Wheezing (bronchospasm) has been reported in less than 1 of 100 patients. See **Warnings.**

Gastrointestinal: Diarrhea has occurred in about 5 of 100 patients. Nausea, gastric pain, constipation, flatulence, and heartburn have been reported in 1 of 100 or less.

Allergic: Pruritus has occurred in less than 1 of 100 patients.

Miscellaneous: Peyronie's disease has been reported in less than 1 of 100,000 patients.

The oculomucocutaneous syndrome associated with the beta blocker practolol has not been reported with Lopressor during investigational use and foreign marketing experience.

Potential Adverse Effects: In addition, a variety of adverse effects not listed above have been reported with other beta-adrenergic blocking agents and should be considered potential adverse effects of metoprolol.

Central Nervous System: Reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Cardiovascular: Intensification of AV block (see **Contraindications**).

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Allergic: Erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Miscellaneous: Reversible alopecia.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

Dosage and Administration Dosage of Lopressor should be individualized. The usual initial dose is 50 mg twice daily whether used alone or added to a diuretic. The dosage may be increased at weekly (or longer) intervals until optimum blood pressure reduction is achieved. In general, the maximum effect of any given dosage level will be apparent after one week of therapy. Usual maintenance dosage is approximately 100 mg twice a day, with a range of 100 to 450 mg per day. Dosages above 450 mg per day have not been studied. While twice-daily dosing is effective and can maintain a reduction in blood pressure throughout the day, some patients, especially when lower dosages are used, will experience a modest rise in blood pressure toward the end of the 12-hour dosing interval. This can be evaluated by measuring blood pressure near the end of the dosing interval to determine whether satisfactory control is being maintained throughout the day. If control is not adequate, a larger dose, or three times daily therapy, may achieve better control. Beta$_1$ selectivity diminishes as dosage of Lopressor is increased.

This drug should be stored at controlled room temperature and protected from moisture.

How Supplied Tablets of 50 mg (capsule-shaped, scored, light red, film-coated) and 100 mg (capsule-shaped, scored, light blue, film-coated) are supplied in bottles of 100 and 1,000 and Unit Dose Packages of 100.

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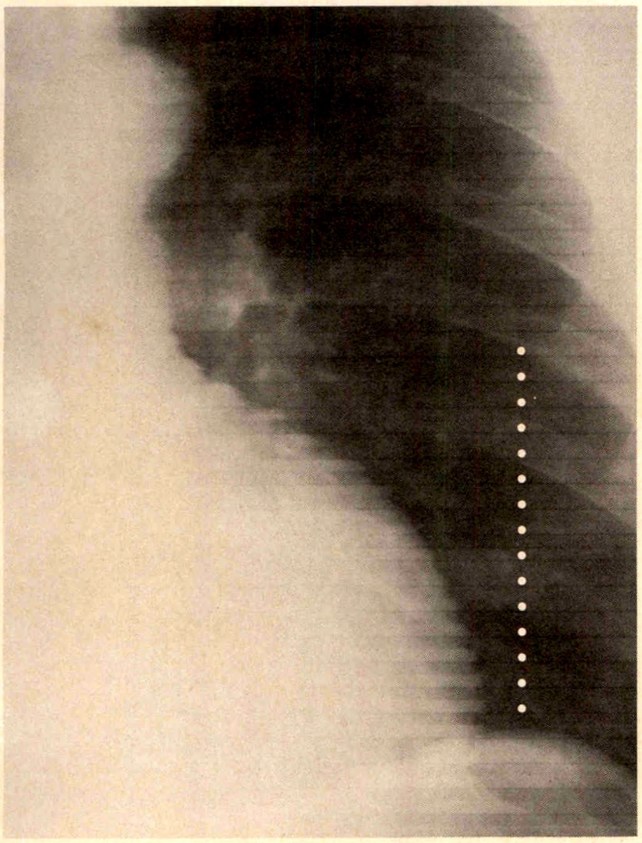

This IRS x-ray shows an asynergistic contraction. Systolic strips are marked in this image with white dots, clearly illustrating normal motion in the basal segment, hypokinesis in the lateral wall and paradoxical motion in the apex.

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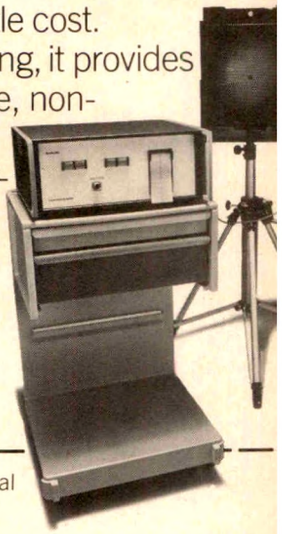

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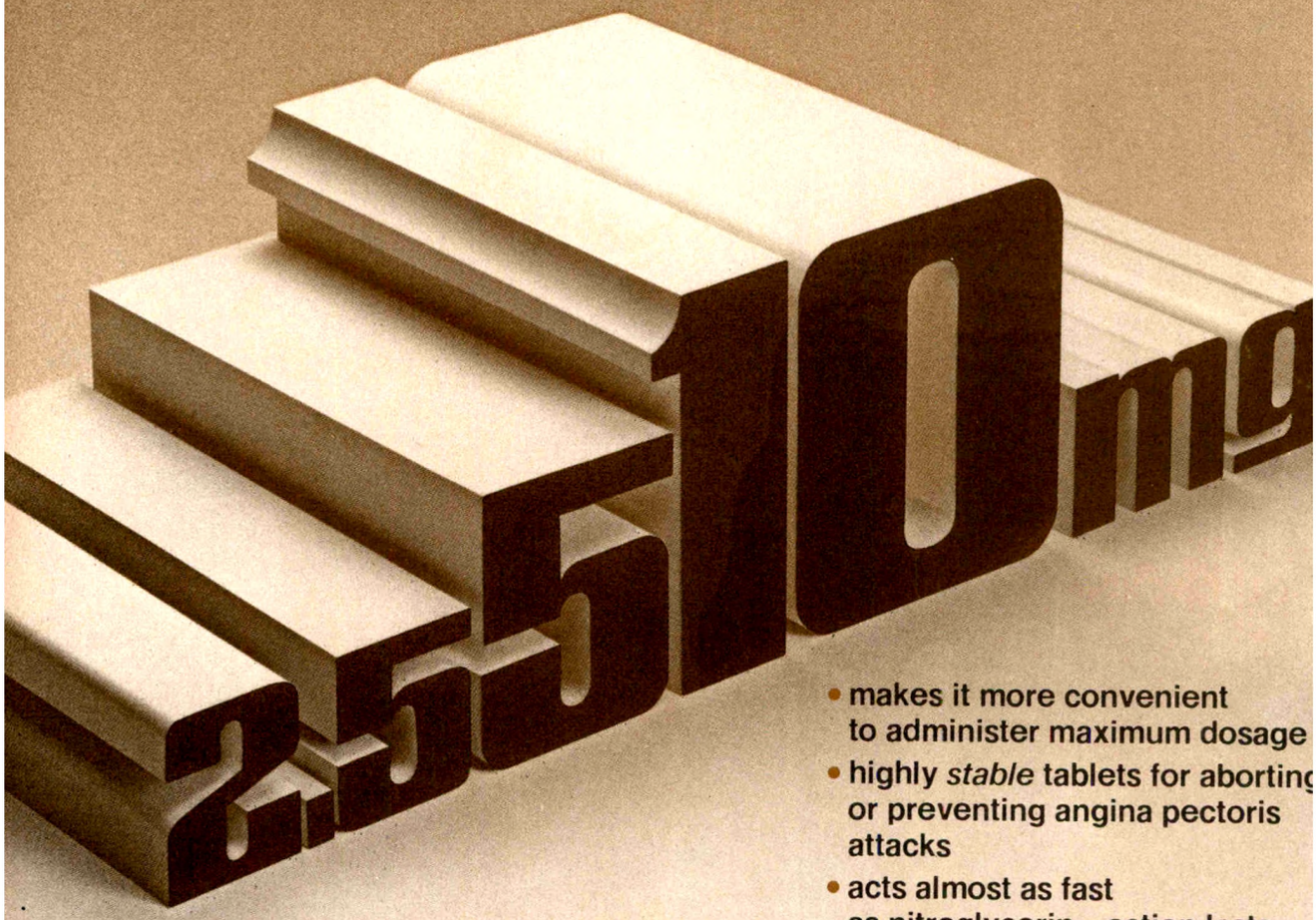

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Hereditary Dysplasia of the Pulmonary Valve in Beagle Dogs

Pathologic and Genetic Studies

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Pathologic and genetic studies were conducted in a colony of beagle dogs with pulmonary stenosis. The pulmonary valve lesions were shown in 70 affected dogs to consist of thickening, fusion and hypoplasia of valve leaflets, which occurred in varying degrees of severity and in various combinations. The gross anatomic structure of the pulmonary valve in some affected dogs resembled that seen in "typical" pulmonary stenosis in human beings; in others it was similar to what has been called pulmonary valve dysplasia. Both types, and intermediate forms, occurred in members of the same litter, indicating that these two types of pulmonary valve deformity are not separate etiologic or developmental entities in the beagle. Pulmonary valve atresia was present in two pups. Light and electron microscopic examination of affected and normal valves indicated that valve thickening, the most prominent feature of the valve abnormality, was due to an increase in the thickness of the valve spongiosa. Blood vessels and sinuses lined with endothelium were common in affected leaflets. We propose that the term *hereditary pulmonary valve dysplasia* be used to describe the entire range of pulmonary valve abnormalities in this hereditary defect of beagles.

Genetic studies, including matings of affected to affected, outcrosses, F_1 crosses and repeated backcrosses showed that pulmonary valve dysplasia is not inherited as a simple Mendelian trait. Genes at more than one locus predispose to abnormal development of the pulmonary valve. The risk of pulmonary valve dysplasia increased with inbreeding, indicating that homozygosity for specific alleles at these loci increases the probability of abnormal development. There is no evidence in affected beagles that other body systems are involved. The genetic data in beagles are consistent with available evidence concerning genetic factors involved in isolated pulmonary stenosis in human beings.

In human beings, congenital stenosis of the pulmonary valve is considered to occur in two major forms. In the "typical" form, the valve leaflets are fused but not markedly thickened, producing a dome-shaped valve with a central orifice. A less common form of valvular pulmonary stenosis, referred to as *pulmonary valve dysplasia,* is characterized by marked thickening of the pulmonary valve leaflets without fusion; obstruction to right ventricular outflow results from crowding of the valve orifice by the thickened, inflexible leaflets.[1] It is not clear whether these two forms of pulmonary valve abnormality represent variations in the expression of a common developmental disturbance or are separate entities. Nor are the underlying causes of pulmonary stenosis of either type well understood.

Epidemiologic and family studies of congenital heart disease in the dog conducted in the 1960s detected a hereditary form of pulmonary valve stenosis in beagles.[2] Affected dogs and their close relatives were subsequently obtained from owners and breeders and used to form a breeding colony in which the clinical, pathologic and genetic features of the condition could be studied in detail. The purposes of this paper

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are (1) to compare this animal model with others previously reported, (2) to examine the gross and histologic abnormalities associated with pulmonary valve lesions in this model, and (3) to investigate the mode of inheritance of pulmonary valve lesions.

Methods

Pedigree and breeding data: Beagles with pulmonary stenosis were donated for study by owners and breeders after a diagnosis of congenital heart disease was made by clinical examination at the University of Pennsylvania Small Animal Hospital. The diagnosis was confirmed by cardiac catheterization and angiocardiography. Examination of pedigrees obtained with the dogs used to form a breeding colony disclosed that some of the affected animals had common ancestors within five generations, while others did not. A series of breeding experiments was performed, consisting of the following matings: (1) affected × affected related (coefficients of inbreeding of offspring ranged from 0.125 to 0.375); (2) affected × affected unrelated (no common ancestors within five generations, coefficient of inbreeding zero); (3) affected × normal beagle with no known relation to beagles with pulmonary stenosis (this mating produced an F_1 generation of offspring); (4) normal F_1 × normal F_1 (this mating of F_1 offspring among themselves produced the F_2 generation); (5) backcross of normal F_1 female dog to an unrelated affected male dog (coefficient of inbreeding zero); (6) backcross of normal F_1 female dog to her affected sire (coefficient of inbreeding 0.25); (7) backcross of normal female dog of mating 6 to her sire-grandsire (coefficient of inbreeding 0.375).

Case material: A total of 303 pups were produced by 69 matings. Of these, 206 died or were killed before cardiac catheterization and were studied primarily by postmortem methods. The remaining 97, of which 22 were affected, were studied by cardiac catheterization and angiocardiography as well as pathologic methods. Four dogs with typical clinical signs of pulmonary stenosis are still living.

Final classification of the phenotypes of parents and offspring for the genetic analysis was made by postmortem examination of the heart, except in four dogs that are still living. These are the offspring of dogs with pulmonary stenosis and have moderate degrees of pulmonary valve stenosis with angiographic features within the range of those observed in closely related dogs examined post mortem. All affected parents used in test matings had moderate to severe pulmonary valve stenosis with thickening and varying degrees of fusion or hypoplasia of valve cusps, or both.

TABLE I

Distribution of Gross Lesions of the Pulmonary Valve Among 70 Beagles With Pulmonary Valve Dysplasia

	Dogs	
	n	%
Thickening only	18	25.7
Hypoplasia only	0	0
Fusion only	0	0
Thickening and hypoplasia	23	32.9
Thickening and fusion	15	21.4
Fusion and hypoplasia	0	0
Thickening, fusion and hypoplasia	14	20.0
Total	70	100.0

Dogs were housed in a temperature-controlled indoor colony in accordance with standard procedures used in the humane care and treatment of laboratory animals.[3] There was no known exposure to teratogenic agents. The diet consisted of Wayne dog meal with added cooked meat byproducts. Breeding was performed by artificial insemination immediately after collection of the semen. Pups were born and raised in pens with supplemental heat provided by brooder heat lamps during the first 4 weeks.

Pathologic studies: Those pups that died or were killed with barbiturate overdose underwent a complete gross autopsy examination. The hearts were examined in detail under a dissecting microscope after fixation in 10 percent buffered formalin. Histologic sections of the pulmonary valve were prepared in selected hearts and stained with hemotoxylin-eosin and in some cases with Movat's pentachrome stain. Pulmonary valves prepared for electron microscopic study were fixed immediately after death in a 2.5 percent glutaraldehyde-formalin solution, embedded in Spurr's medium[4] and stained with lead citrate-uranyl acetate. Surviving pups were anesthetized with pentobarbital sodium or halothane and studied by cardiac catheterization and angiocardiography at 8 to 12 weeks of age. Those not retained for further breeding studies were killed with a barbiturate overdose and subjected to autopsy examination.

Analysis of data: Pedigree information, together with pathologic and other data on each dog, was coded and stored on magnetic tape. Retrieval and analysis was assisted by a laboratory digital computer (Linc 8, Digital Equipment Corp., Maynard, Massachusetts).

Results

An appreciation of the spectrum of pulmonary valve anomalies observed in the offspring of matings is essential to the interpretation of clinical and genetic findings. Therefore, the results of pathologic studies will be presented first.

Pathologic Features

Of the 303 pups produced in 69 test matings, 74 (24.4 percent) had malformations of the pulmonary valve. Of these, 70 specimens were available for complete postmortem examination and form the basis of the following description of the pulmonary valve deformity.

Gross anatomy of affected valves: In general, the pulmonary valve anulus was normal or slightly reduced in size. Abnormalities of the pulmonary valve leaflets consisted of thickening, hypoplasia or fusion. These lesions occurred in various combinations and in varying degrees of severity (Table I), and all were seen in animals belonging to the same sibship.

All of the affected dogs had some degree of thickening of the pulmonary valve leaflets. The anterior, right and left leaflets were involved with about equal frequency, and in a given dog more than one of the three leaflets was usually affected. Of the 70 affected dogs, 4 had one, 24 had two and 42 had three thickened leaflets. The degree of thickening ranged from a slight increase in cross-sectional area (Fig. 1B) to bulky, nonflexible, cushion-like valve leaflets that nearly filled the valve orifice (Fig. 1D). The surfaces of the thickened leaflets, particularly the luminal surfaces and the free margins,

were often covered with small, irregular nodules (Fig. 1, C and D).

Valve leaflets were classified as hypoplastic when they were smaller than those of normal control dogs of the same age. The degree of hypoplasia varied from a slight reduction in overall size to complete absence of a leaflet (Fig. 2). Usually, only one or two of the leaflets were involved, and the reduction in size was readily apparent on comparison with others in the same valve. Affected leaflets were often misshapen as well as reduced in size. Among 37 dogs with hypoplastic leaflets, 27 had one, 5 had two and 5 had three hypoplastic leaflets. The leaflets most often involved were the left (29 dogs) and anterior (17 dogs). The right leaflet was hypoplastic in six dogs.

Pulmonary valve leaflets were considered fused when adjacent leaflets did not insert separately on the intimal surface of the pulmonary artery (fusion of commissures). The degree of fusion varied from slight (less than one fourth of the valve margins involved) (Fig. 3A) to almost complete fusion involving the entire margin and resulting in a small central orifice (Fig. 3C). The three commissures were affected with nearly equal frequency, and usually more than one commissure was

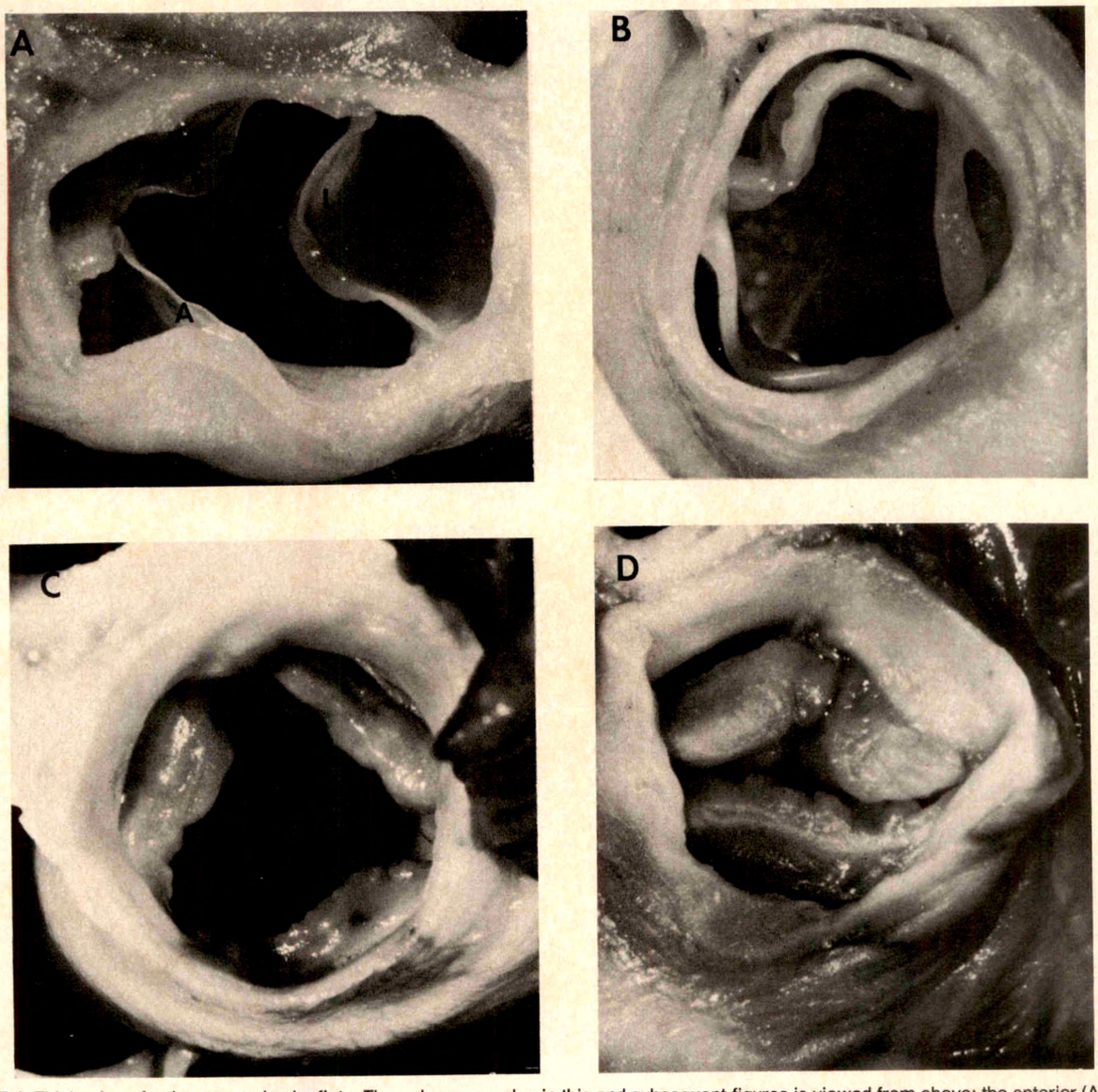


FIGURE 1. Thickening of pulmonary valve leaflets. The pulmonary valve in this and subsequent figures is viewed from above; the anterior (A) leaflet is located toward the **bottom** of the figure; the left (L) leaflet is at the **upper right** and the right (R) leaflet at **upper left. A,** pulmonary valve of a 3 month old female poodle with a normal heart. Note the thin translucent nature of the leaflets. **B**, pulmonary valve of a 3 month old female beagle with mild thickening of all leaflets. The right leaflet has irregular nodules along its free edge. **C**, moderate thickening of all three pulmonary valve leaflets in a 3 day old female beagle. The valve surface is irregular. **D**, marked thickening of all leaflets in a newborn male beagle. The leaflets consist of stiff "pads" that nearly occlude the pulmonary valve orifice.

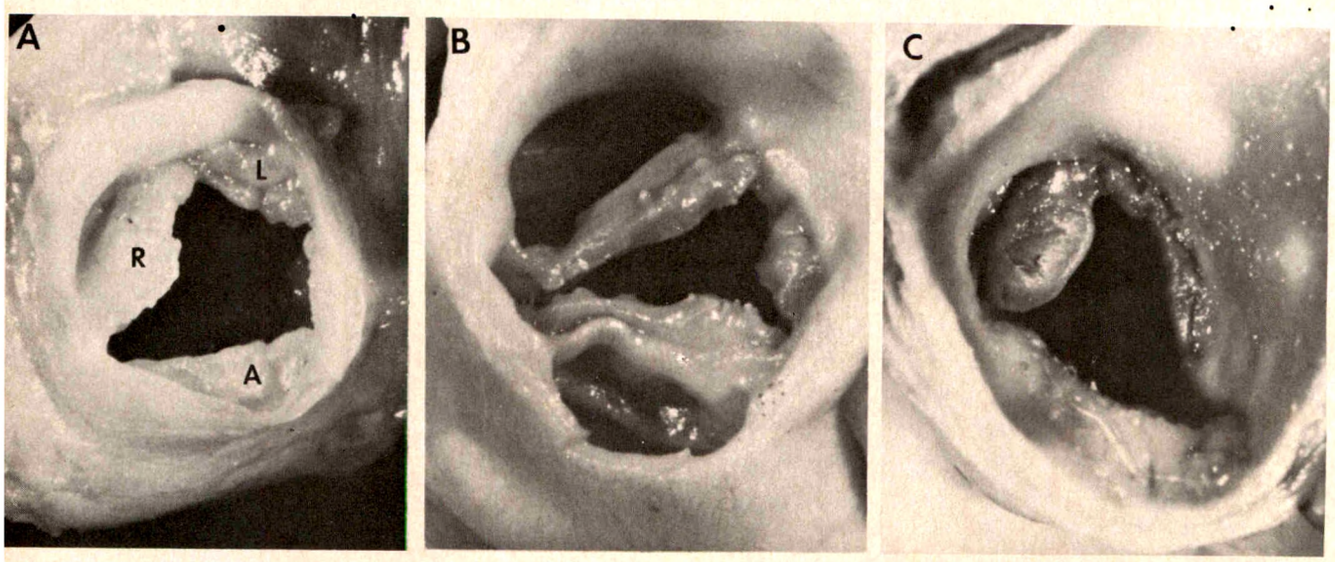


FIGURE 2. Hypoplasia of valve leaflets. **A**, thickening of all leaflets and hypoplasia of the left leaflet in a newborn male beagle. **B**, thickening and hypoplasia of the left leaflet in an 8 week old male beagle. The left leaflet is reduced to a small "pad" with no sinus of Valsalva. **C**, thickening of all leaflets and hypoplasia of the left and right leaflets in a newborn male beagle. The left leaflet is reduced to a small ridge of tissue, while the right leaflet is markedly thickened, irregular and reduced in size. The anterior leaflet consists of a thick ridge with no sinus of Valsalva. Abbreviations as in Figure 1.

involved. In some dogs, the pulmonary valve consisted of a diaphragm with a central orifice, with no evidence of separate valve leaflets (Fig. 3D). Two pups that died at 1 and 4 days, respectively, had complete atresia of the pulmonary valve, a hypoplastic valve anulus and a small cord-like main pulmonary artery. Pulmonary blood flow occurred through enlarged bronchial arteries.

Other cardiovascular malformations: Three of the 70 dogs with anomalous pulmonary valves had other cardiovascular malformations as well. One had a small subcristal ventricular septal defect and a small septum secundum atrial septal defect. The second had a small subscristal ventricular septal defect, and the third had a small patent ductus arteriosus. Cardiovascular malformations were not found in the 229 offspring that had normal pulmonary valves.

Except for the two pups with small ventricular septal defects, there were no anomalies of the crista supraventricularis as are found in Keeshond dogs with pulmonary stenosis associated with abnormal development of the conotruncal septum.[5,6] The papillary muscle of the conus was consistently present, and no aneurysms of the crista supraventricularis or evidence of the conal septum fusion line were seen (Fig. 4).

Histologic features of anomalous pulmonary valves: The histologic anatomy of the normal canine pulmonary valve is similar to that of the normal human pulmonary valve as described by Gross and Kugel.[7] In longitudinal section the valve is elongated with a wide base at the site of myocardial attachment and a slender projection into the arterial lumen (Fig. 5A). In transverse section the center of the valve cusp is narrow and is composed of three layers: the fibrosa, the valve spongiosa and the ventricularis (Fig. 5B). In dogs, as in human beings, the fibrosa is the layer located on the arterial aspect of the valve. It is covered by a layer of flat endothelial cells, may contain elastic fibrils (seen in Movat pentachrome-stained sections) and is not sharply separated from the underlying valve spongiosa. The central area, the valve spongiosa, varies in thickness and contains loose fibrillar material, fragments of collagen and widely separated cells. The ventricularis is the fibroelastic layer present on the ventricular aspect of the valve and is covered by a layer of flat endothelial cells. In transverse section of the canine valve cusp periphery, where lateral attachment to the arterial wall occurs, the valve often has projections into the sinus and is broad because of a relative increase in the dimensions of the valve spongiosa, which may have a very loose architecture. A fibroelastic connective tissue band, which is closely associated with the ventricularis in the central cusp area, crosses the valve spongiosa to become aligned along the fibrosa near the lateral attachment of the valve. Blood vessels or empty spaces lined by endothelial cells were not present in normal canine pulmonary valves.

The dysplastic valves appeared thickened in both longitudinal (Fig. 6A) and transverse (Fig. 6B) sections because of the increase in the dimensions of the valve spongiosa; many valves were as wide or wider in the central cusp area as in their periphery. Most of the thickened spongiosa consisted of loosely arranged connective tissue containing cells similar to those observed in the spongiosa of normal pulmonary valves. Also present within the spongiosa were bands of fusiform cells in a dense and regular collagen network (Fig. 6B). In transverse sections these bands were usually present in the middle of the valve and were parallel to the cusp edge. Blood-filled spaces in cross section and empty endothelial-lined spaces were present in at least one cusp of all affected animals (Fig. 6 A and B). The fibroelastic band of the ventricularis was fragmented,

reduced or absent in most cusps. The endothelial cells observed along the valve edges appeared similar in both affected and control animals.

Electron microscopy: On electron microscopy no consistent differences were observed between normal and dysplastic valves other than those described at the light microscopic level. Most cells were elongated with relatively large nuclei and prominent nucleoli (Fig. 7). The endothelial cells of the valve margin had a few microvilli projecting into the vessel lumen. The matrix consisted of short bands of collagen and granular electron-dense material loosely arranged between the cells.

Clinical Features

The primary objective of this report is to describe the pathologic and genetic features of pulmonary valve dysplasia in beagle dogs. However, the clinical features observed in the 18 affected dogs that were studied by cardiac catheterization, angiocardiography and postmortem methods will be briefly summarized for comparison with clinical features of pulmonary stenosis in human beings.

Five dogs with slightly thickened but unfused pulmonary valve leaflets had a systolic murmur in the pulmonary valve area on auscultation, but had little or no other signs of pulmonary outflow obstruction (nor-

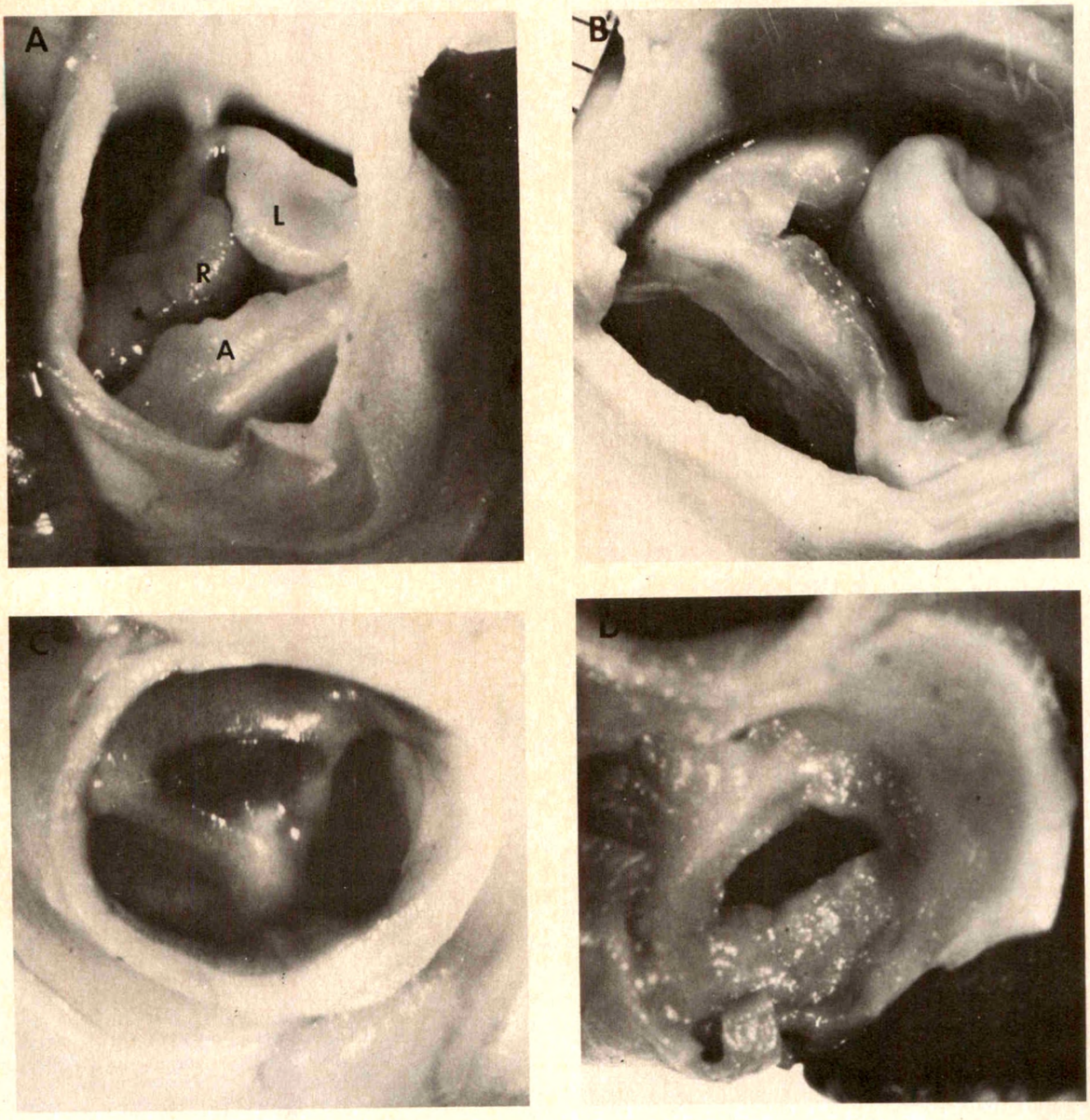
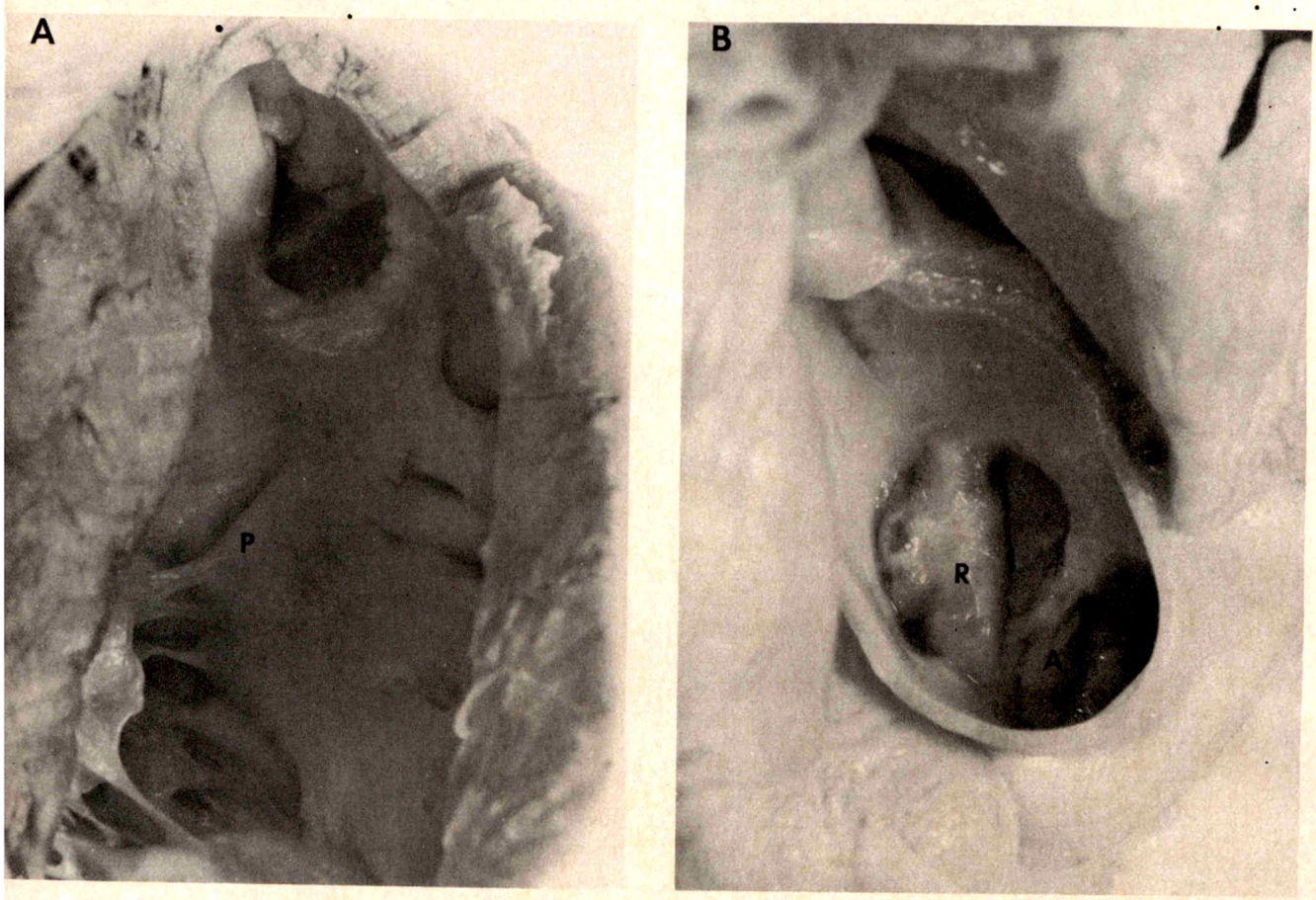


FIGURE 3. Fusion of pulmonary valve leaflets. **A**, marked thickening with minimal fusion of the right and left leaflets in a 3 day old male beagle. **B**, thickening and a more advanced degree of fusion between the anterior and right leaflets of the pulmonary valve in an 11 year old female beagle. **C**, thickening and advanced fusion of all valve leaflets in a 6 week old male beagle. **D**, the pulmonary valve in a 1 day old female beagle consists of a thick diaphragm without differentiation of leaflets. Abbreviations as in Figure 1.



IGURE 4. Outflow tract and pulmonary valve of an 8 year old female beagle with severe pulmonary stenosis. **A**, right ventricular outflow tract showing ell developed papillary muscle of the conus (P), muscular crista supraventricularis and thickened pulmonary valve ring (**top**). B, pulmonary valve iewed from above. The right (R) and anterior (A) leaflets are thickened and fused. The anterior leaflet has a sinus of Valsalva, but the right leaflet oes not. The left leaflet is hypoplastic, resulting in a small, eccentric pulmonary valve orifice.

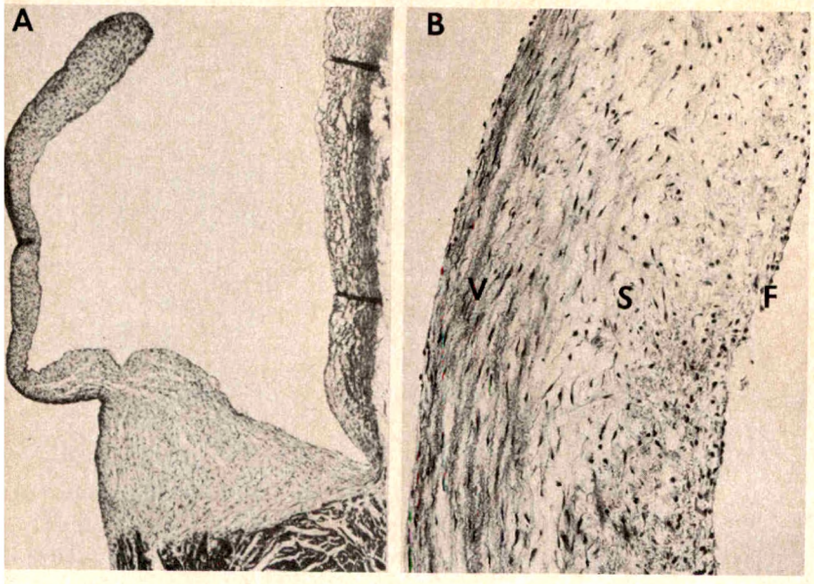


FIGURE 5. Normal pulmonary valve. **A**, light photomicrograph of a normal pulmonary valve cusp in longitudinal section. The valve has a wide base of attachment to the myocardium and a slender elongate projection into the arterial lumen. **B**, light photomicrograph of a normal pulmonary valve cusp in transverse section. The valve is composed of three layers: the fibrosa (F), the spongiosa (S) and the ventricularis (V). (Hematoxylin-eosin ×70 (**A**) and ×200 (**B**), reduced by 33 percent.)

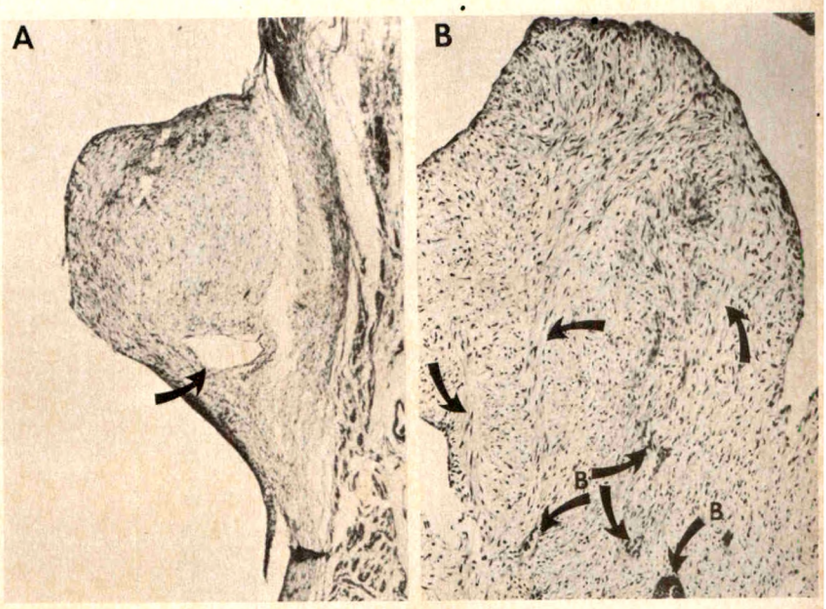


FIGURE 6. Dysplastic pulmonary valve. **A**, light photomicrograph of a dysplastic pulmonary valve in longitudinal section. The valve is short and thick and contains a large space lined by endothelial cells (**arrow**). **B**, light photomicrograph of a dysplastic pulmonary valve in transverse section. The valve is wide and contains bands of fusiform cells and collagen (**arrows**) as well as blood-filled spaces (B). (Hematoxylin-eosin ×96 (**A**) and ×145 (**B**), reduced by 32 percent.)

mal electrocardiograms and chest roentgenograms). Eleven dogs with moderate to severe thickening or fusion of leaflets, or both, had electrocardiographic signs of right ventricular hypertrophy, a loud ejection-type systolic murmur in the pulmonary valve area, radiographic evidence of right ventricular enlargement and poststenotic dilatation of the pulmonary artery. Two other dogs with a thick, diaphragm-like pulmonary valve had these signs but also had a decrescendo diastolic murmur over the pulmonary valve area and right ventricle, indicating the presence of pulmonary valve insufficiency as well as stenosis.

On cardiac catheterization, the dogs with the mildest degrees of pulmonary valve abnormality had normal right ventricular pressure and lacked a significant systolic pressure gradient across the pulmonary valve, even though grade 1/6 to 2/6 systolic ejection-type murmurs characteristic of pulmonary stenosis were present. In more severely affected animals there was clear evidence of obstruction at the level of the pulmonary valve, with right ventricular systolic pressure as high as 152 mm Hg in one animal that died at age 3 years with congestive heart failure.

Angiocardiographic abnormalities were absent in dogs with only slight degrees of valve thickening. Angiocardiograms in dogs with mild forms of dysplasia in some cases revealed thickening of pulmonary valve leaflets (Fig. 8A) or malformed sinuses of Valsalva (Fig. 8B), or both, without doming of the pulmonary valve or a central jet. Moderately to severely affected dogs had a variety of angiocardiographic abnormalities. Poststenotic dilatation of the major pulmonary artery was consistently present. When leaflets were fused but not markedly thickened, the appearance resembled that in "typical" pulmonary valve stenosis in man, with a well defined central jet and doming of the pulmonary valve during systole (Fig. 8C). Dogs with very thickened and fused valves had a thick radiolucent diaphragm that moved very little during the cardiac cycle, with a central systolic jet (Fig. 8D). Thus, clinically as well as pathologically, the spectrum of abnormalities varied from that characteristic of the "typical" form of pulmonary valvular stenosis in man to that described in recent years as pulmonary valve dysplasia.[1,8–11]

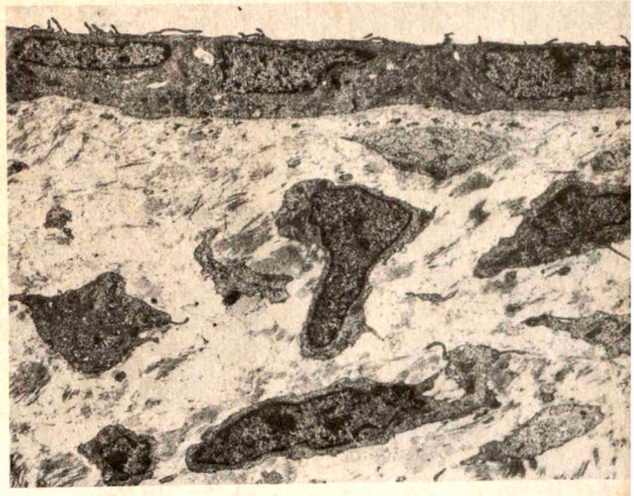
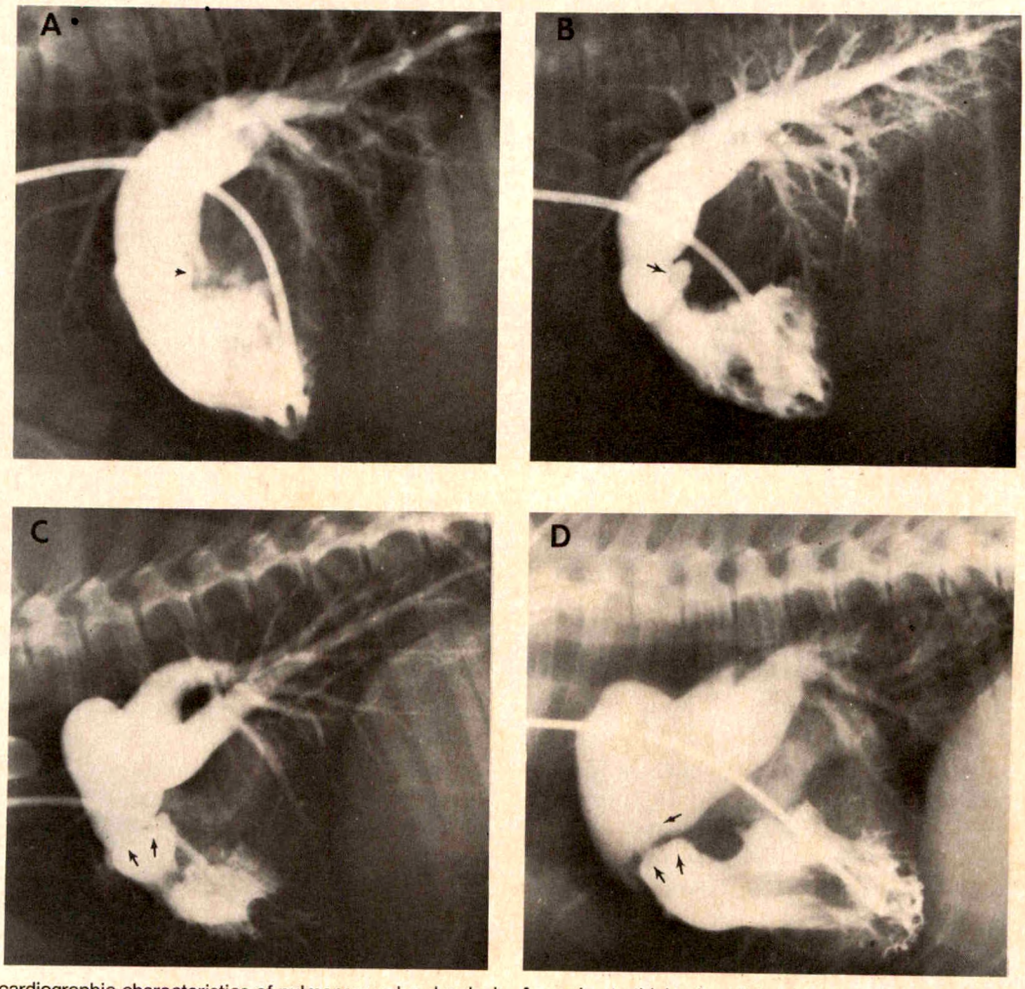


FIGURE 7. Normal pulmonary valve. Electron photomicrograph of the margin of a normal pulmonary valve. The endothelial cells have several microvilli; the inner cells contain large nuclei with relatively little cytoplasm. The matrix consists of collagen and electron-dense granular material loosely arranged around the cells. (Lead citrate-uranyl acetate ×4,750, reduced by 33 percent.)



IGURE 8. Angiocardiographic characteristics of pulmonary valve dysplasia. **A**, moderate thickening of the right and anterior leaflets of the pulmonary alve in a 12 week old male beagle. The thickened right leaflet can be seen as a filling defect which changes little in appearance from one phase f the cardiac cycle to another (**arrow**). There was no significant pressure gradient across the pulmonary valve. **B**, 10 week old female beagle with ypoplasia of the left pulmonary valve leaflet and distortion of the sinus of Valsalva (**arrow**). There was no significant pressure gradient across ıe pulmonary valve. **C**, 1 year old male beagle with moderate pulmonary valve stenosis due to mild thickening and fusion of valve leaflets. Doming f the pulmonary valve during ventricular systole is clearly visible (**arrows**). Right ventricular pressure was 78/0 and pulmonary arterial pressure 8/6 mm Hg. The dog survived to age 11 years as a breeding animal. **D**, pulmonary stenosis and insufficiency in an 8 year old female beagle with ıarked thickening and fusion of valve leaflets. The thickened, "diaphragm-like" pulmonary valve (**lower arrows**) moves little from one phase of ıe cardiac cycle to another. A systolic jet is evident (**upper arrow**). Right ventricular pressure was 92/0 mm Hg.

enetic Analysis

Grading of pulmonary valve dysplasia: It is aparent from the results of our pathologic and clinical udies that the underlying developmental abnormality ads to a wide spectrum of pulmonary valve anomalies ut usually does not affect other portions of the heart. or purposes of genetic analysis, the entire spectrum ill be regarded collectively as pulmonary valve dysasia, with the degree of dysplasia classified into two ades: *Grade 1* indicates slight thickening of pulmoıry valve leaflets with little or no fusion or hypoplasia, oducing minimal or no demonstrable pulmonary ıtflow obstruction. *Grade 2* indicates moderate to vere thickening of pulmonary valve leaflets, usually th fusion or hypoplasia, or both, producing moderate severe pulmonary outflow obstruction.

Among the 303 offspring of 69 test matings, there were 74 affected pups, 19 of which had grade 1 and 55 grade 2 dysplasia. The incidence of the defect was similar in male (39 of 157 or 24.8 percent) and female animals (35 of 146 or 24.0 percent).

Results of test matings (Table II): The proportion of affected pups was highest when two dysplastic dogs were mated, but was greater when the parents were related as parent-offspring or uncle-niece (58.8 percent) than when they were unrelated* (27.6 percent) (chi-square = 4.391, df = 1, $p < 0.05$). Eight outcrosses of dogs with pulmonary valve dysplasia to normal unre-

* Although it is recognized that the dogs may have have been distantly related, there were no common ancestors within at least five generations as determined from the pedigrees available.

TABLE II

Genetic Studies of Hereditary Dysplasia of the Pulmonary Valve in Beagle Dogs

Mating Type*	Litters (n)	Offspring (n)	Normal		Dysplasia					
					Grade 1		Grade 2		Total	
			n	%	n	%	n	%	n	%
Dysplastic × dysplastic										
Unrelated (Fx = 0.00)	8	29	21	72.4	3	10.3	5	17.2	8	27.6‡
Related (Fx ≥ 0.125)	4	17	7	41.2	1	5.9	9	52.9	10	58.8‡
Dysplastic × normal unrelated										
F_1	8	50	50	100.0	0	0.0	0	0.0	0	0.0
F_2	8	42	39	92.9	2	4.8	1	2.3	3	7.1
Backcrosses										
Normal F_1 female × unrelated dysplastic male (Fx = 0.00)	8	42	34	80.9	1	2.4	7	16.7	8	19.1‡
Normal F_1 female × dysplastic sire (Fx = 0.250)	23	94	63	67.0	8	8.5	23	24.5	31	33.0‡
Normal F_1 BC female × dysplastic sire-grandsire (Fx = 0.375)	10	29	15	51.7	4	13.8	10†	34.5	14	48.3‡
All matings	69	303	229	75.6	19	6.3	55	18.1	74	24.4

* Reciprocal crosses pooled. All parents with dysplasia of the pulmonary valve had grade 2 dysplasia. † Includes two pups with pulmonary valve atresia. ‡ Within these mating types, the offspring of two related dogs had pulmonary valve dysplasia more often than those of unrelated dogs ($p < 0.05$).

BC = backcross; Fx = coefficient of inbreeding of offspring; grade 1 dysplasia = slight thickening of pulmonary valve leaflets with little or no fusion or hypoplasia, producing minimal or no pulmonary outflow obstruction; grade 2 dysplasia = moderate to severe thickening of the pulmonary valve leaflets, usually with fusion or hypoplasia or both, producing moderate to severe pulmonary outflow obstruction; unrelated = no common ancestors within five generations.

lated beagles produced 50 pups, none of which was affected. These F_1 offspring were mated among themselves to produce 42 pups in the F_2 generation, 3 (7.1 percent) of which had dysplastic pulmonary valves.

Backcrosses of phenotypically normal offspring of beagles with valve dysplastic beagles to beagles with valve dysplasia were of three types: crosses to beagles with dysplasia that were unrelated, crosses to a parent with dysplasia and second backcrosses. In the latter case, a normal female offspring of the first backcross was mated to the male that was her sire-grandsire (Table II). Although the parental phenotypes in these three types of backcrosses were equivalent (normal × affected), the proportion of affected offspring varied, being lowest when the parents were unrelated (19.1 percent) and highest when the genes of an affected sire were concentrated by two successive backcrosses (48.3 percent) (chi-square = 6.795, df = 2, $p < 0.05$).

These findings allow the following conclusions:

1. Outcrosses of affected dogs to normal unrelated beagles failed to produce any affected offspring, indicating that the gene or genes involved do not produce pulmonary valve dysplasia when present in heterozygous state. In this sense the defect can be considered "recessive."

2. It is clear that a single recessive gene with full penetrance is not an adequate explanation, because in matings of affected to affected beagles only 28 to 58 percent of the offspring were affected.

3. The risk of pulmonary valve dysplasia in backcross matings increased with the degree of inbreeding, indicating that homozygosity for alleles identical by descent increases the risk of pulmonary valve dysplasia.

4. Matings of affected to affected produced a higher proportion of affected pups when the parents were related than when they were not, again indicating that increased risk is conferred by increased homozygosity. However, in this case, it can be further inferred that two affected dogs, when unrelated, may be homozygous at different loci affecting the development of pulmonary valve dysplasia. If this were not true, no inbreeding effect would be observed.

Discussion

Pulmonary valve stenosis in human beings compared with the beagle dog: In the "typical" form of pulmonary valve stenosis in man, the valve usually has three fused commissures and a restricted central orifice, the size depending on the degree of fusion. A central jet representing rapid flow through the orifice and "doming" of the valve in ventricular systole are often seen in angiocardiograms.[11] In a rare form of pulmonary stenosis in human beings, usually referred to as pulmonary valve dysplasia, the three valve leaflets are markedly thickened and there is no commissural fusion, the obstruction resulting from crowding of the valve orifice by the redundant valve tissue; the anulus of the pulmonary valve is usually normal or slightly hypoplastic.[1,8–10] In angiocardiograms, doming of the valve is not seen and the thickened leaflets appear as filling defects in the sinuses of Valsalva.[8,11]

The etiologic and developmental relations between typical pulmonary stenosis and pulmonary valve dysplasia in human beings are unknown. Although it might be assumed that they are separate entities, this is clearly not so in the beagle dog. Our pathologic studies indicate that the same underlying genetic and developmental abnormality produces a spectrum of varying degrees of thickening, fusion and hypoplasia of valve leaflets. Some combinations result in a valve anomaly that closely resembles typical pulmonary stenosis in human beings; othere are characteristic of what has been called pulmonary valve dysplasia.[1] Indeed, both

orms and others intermediate between them were observed within a single litter. A common etiologic and developmental mechanism may underlie the different anatomic forms of pulmonary stenosis in man as well as dog. Koretzky et al.[1] reported a series of 16 patients with pulmonary valve dysplasia. Four of these patients had one or more close relatives with pulmonary stenosis, and in each family the other affected persons had the typical form.

Pulmonary valve dysplasia in the beagle: We prefer to group the entire spectrum of valve abnormalities in the beagle under the term *pulmonary valve dysplasia* because it serves to imply a spectrum of abnormal development produced by a common mechanism. Dysplastic pulmonary valve leaflets in the beagle are characterized primarily by an increase in the thickness of the spongiosa and fragmentation of the fibroelastic band of the ventricularis. Based on our observations at the light and electron microscopic levels, the cellular, fibrillar and matrix elements of the spongiosa of dysplastic valves do not appear to differ qualitatively from those of the normal valve. These findings suggest a coordinated overproduction of normal elements or a failure of the normal processes involved in conversion of the cushion-like embryonic valve primordia to the delicate leaflets present in the differentiated valve. The presence of blood vessels and sinuses in the thickened leaflets, a feature also noted in pulmonary valve dysplasia of human beings,[1] may be a primary abnormality or could be a secondary effect consequent to the increased circulatory requirement of greater valve tissue mass.

The precise nature of the underlying developmental disturbance in pulmonary valve dysplasia of beagles is not yet known, but it appears to be confined to the pulmonary valve anlagen, in contrast to the pulmonary valve anomalies found in Keeshond dogs.[5] The range of pulmonary valve malformations is similar to that in beagles, but in the Keeshond dog they are always accompanied by ventricular septal defects or minor malformations of the crista supraventricularis. The common basis for the spectrum of defects in the Keeshond dog has been shown to be a hereditary defect producing varying degrees of hypoplasia of the conotruncal septum.[6]

Genetic factors in human pulmonary stenosis: Pulmonary stenosis in human beings usually occurs as an isolated defect, but in recent years it has also been recognized as one of the features of a few rare genetic syndromes. In early studies that did not distinguish the isolated from the syndromal types, Lamy et al.[12] found the incidence of pulmonary stenosis in siblings of affected children to be 3.75 percent. This is about 100 times the incidence rate of pulmonary stenosis in children born in the general population, suggesting that genetic factors are of etiologic importance. There was an increased incidence of consanguineous marriages in the parents of affected children, indicating that homozygosity for a certain gene or genes that behave as recessives may predispose to the defect. Campbell,[13] in a somewhat later study, found a recurrence rate in siblings of 2.2 percent, whereas Sanchez-Cascos[14] removed the nonsyndromal cases from his series and found a rate of 1.5 percent. Combining reported data and their own cases, Nora and Nora[15] recently estimated the recurrence risk of isolated pulmonary stenosis in siblings as 2.0 percent and that for the offspring of patients as 3.5 percent.

Overall, evidence for the importance of genetic factors in causing isolated pulmonary stenosis in man is substantial, but it is evident that the condition is not inherited as a simple Mendelian trait. The risk of recurrence in the offspring and siblings of affected children is too low to be consistent with simple dominant inheritance. Although the increased frequency of consanguineous marriages in parents suggests recessive inheritance, the similar incidence of the defect in siblings and offspring of patients is not consistent with a simple recessive mode of transmission. Nora and Nora[15] and Sanchez-Cascos[14] pointed out that isolated pulmonary stenosis, like some other forms of congenital heart disease in man, is probably inherited as a multifactorial trait. According to this concept, genes at a number of loci (a polygenic system) as well as environmental factors influence the susceptibility to abnormal development, producing discrete malformations when some critical developmental threshold is crossed. Edwards[16] pointed out that the risk of recurrence of a polygenic trait of high heritability in the first degree relatives (parents, offspring and siblings) of affected persons should approximate the square root of the incidence of the defect in the population. This does appear to be true in some common forms of congenital heart disease, including pulmonary stenosis.[14,15]

In human beings, the atypical form of pulmonary valve stenosis referred to as pulmonary valve dysplasia occurs as one of the variable features of the Noonan syndrome, an inherited constellation of defects which also includes facial dysmorphia, small stature and mental retardation.[10,17,18] Although the affected beagle dogs in our studies often had valve anomalies that resemble those in children with the Noonan syndrome, the dogs had no apparent abnormalities of other body systems.

Implications: The results of our experimental matings of beagle dogs with pulmonary stenosis are consistent with the available evidence regarding the inheritance of isolated pulmonary stenosis in man. In both species more than one locus is involved and the risk of affected offspring is increased by inbreeding, indicating that the genes that condition abnormal development have a greater effect when in a homozygous state. In beagles it is apparent that all affected dogs are not homozygous at the same loci, since affected × affected matings produced a significantly higher proportion of affected pups when the parents were closely related than when they were not.

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Management of Symptomatic Infants With Anomalous Origin Of the Left Coronary Artery From the Pulmonary Artery

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There is disagreement concerning the optimal management of infants with congestive heart failure due to anomalous origin of the left coronary artery from the pulmonary artery. This report describes treatment in 23 such patients who had congestive heart failure before age 6 months. Eight patients had an operation in the 1st year of life and only two (25 percent) of these patients survived. Fifteen patients received initial medical treatment, and operation was delayed until an average age of 7.5 years; 13 (87 percent) of these patients survived. The two patients who survived early operation are still alive at an average age of 2.5 years. The 13 survivors in the medical group are still alive at an average age of 14.5 years. The age at onset and the severity of congestive heart failure were similar in the two groups. The frequency of the electrocardiographic pattern of myocardial infarction was similar in both groups. The radiographic cardiothoracic ratio was 0.74 in the surgical and 0.66 in the medical group. In 10 patients the left ventricular ejection fraction was less than 20 percent in the 1st year of life. In 7 of these 10 patients operation was performed before age 1 year and 2 (28 percent) survived; of the 3 patients treated medically, 1 (33 percent) survived.

The outcome of surgical or medical treatment of the infant with anomalous origin of the left coronary artery from the pulmonary artery may be biased by patient selection. In the infants with depressed left ventricular function, the results of surgical and medical treatment are equally disappointing. Because coronary arterial surgery in the 1st year of life in infants with severely depressed myocardial function has an extremely high mortality rate (75 percent) and because many symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery can be treated medically and survive, we recommend delay of operative intervention until at least age 18 months.

Anomalous origin of the left coronary artery from the pulmonary artery occurs in 1 of 300,000 children and constitutes approximately 0.24 percent of all congenital cardiac anomalies.[1] Despite its rarity, anomalous origin of the left coronary artery from the pulmonary artery is an important form of congenital heart disease since the mortality from this lesion has been estimated to be as high as 93 percent in the 1st year of life.[2] Also, in light of recent advances in cardiovascular operative techniques,[3,4] many investigators[5–11] recommend surgical correction of the lesion early in infancy. However, other investigators[12–14] recommend initial medical management of symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery and delay of surgical intervention until an older age. Disagreement concerning the optimal management of infants with this lesion exists, in part, for two reasons: (1) Many reported series are small with unequal distribution of patients in surgical and medical treatment groups; and (2) there is considerable variation from study to study in the criteria for assigning patients to surgical or medical treatment. At the Texas Children's Hospital we have managed a relatively large number of symptomatic

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TABLE I

Surgical Group

		ECG		Cardio-thoracic	Cardiac Catheterization				Peak Systolic Pressure (mm Hg)			Operation		
Case	Outcome	MI	Age (mo)	Ratio (%)	Age (mo)	LVEDP (mm Hg)	LVEF (%)	Qp/Qs	PA	LV	PA/LV	Age (mo)	Type	PO (mo)
S-1	D	+	3	72	9	10	24	1.03	38	80	0.48	9	I	. . .
S-2	S	+	2	84	3	10	9.2	1.06	35	90	0.39	3	I	48
S-3	S	0	4	68	4	12	15	1.17	40	80	0.50	4	I	2
S-4	D	+	4	70	4	15	13	1.2	24	98	0.24	4	I	. . .
S-5	D	0	6	88	6.5	28	20	1.0	42	100	0.42	6.5	SV	. . .
S-6	D	+	2	68	2	20	20	0.84	28	80	0.35	2	I	. . .
S-7	D	—	—	70	2	15	. . .	. . .	31	70	0.44	2	L	. . .
S-8	D	0	5	69	5	20	19	1.04	38	85	0.45	5	I	. . .
Average	. . .	. . .	3.7	73.6	4.4	16.3	17.2	1.05	34.5	85.4	0.40	4.4	. . .	25

D = died; ECG = electrocardiogram; I = implantation of left coronary artery into aorta; L = ligation of the left coronary artery; LV = left ventricular; LVEDP = left ventricular end-diastolic pressure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PA = pulmonary arterial; PO = months postoperative; Qp/Qs = ratio of pulmonary to systemic blood flow; S = survived; SV = saphenous vein graft.

infants with anomalous origin of the left coronary artery from the pulmonary artery both surgically and medically. The purpose of this study is to review the results of the surgical and medical therapy and attempt to define the optimal management plan for these infants.

Methods

Patients: Between 1955 and March 1980 we evaluated and treated 30 patients with anomalous origin of the left coronary artery from the pulmonary artery. Two of these 30 patients had an associated ventricular septal defect and will not be discussed further.[15] In five other patients symptoms did not develop in infancy, and they will not be discussed further. The remaining 23 patients in whom symptoms of congestive heart failure developed during the first 6 months of life are the subjects of this study.

Diagnosis: All patients had diagnostic cardiac catheterization. All physiologic pressures were measured with use of fluid-filled catheters with zero pressure reference adjusted to the mid chest level. Left ventricular ejection fraction was determined from the anteroposterior left ventricular angiogram using the method of Sandler and Dodge.[16] The quality of the left ventricular cineangiogram was technically adequate to determine ejection fraction in 15 of 23 patients. The presence of a left to right shunt was determined by the appearance of contrast medium in the pulmonary artery after injection into the left ventricle or aorta. The ratio of systemic to pulmonary blood flow was calculated by the Fick method.

Fourteen patients had an M mode echocardiogram. All echocardiography was performed with a Hoffrel model 101 ultrasonascope interfaced to a Honeywell 1856 strip chart recorder. Transducers of 2.25 and 3.5 megahertz were used.

Surgery: All operations were performed using cardiopulmonary bypass and moderate systemic hypothermia (30° C). Starting in April 1977, high potassium cold cardioplegic solution was infused into the aortic root for myocardial preservation. For the purposes of this study "surgical treatment" or "surgical group" is defined as operative intervention before age 1 year and "medical treatment" or "medical group" is defined as no operative intervention or delay of operative intervention until after age 1 year.

Results

All 23 patients in whom symptoms of congestive heart failure developed before age 6 months were treated with appropriate doses of a digitalis preparation and in most cases a diuretic drug.

Surgical Group

Of these 23 patients, 8 had a cardiac operation at less than 1 year of age (Table I). The age at operation ranged from 2 to 9 months (average 4.4). All but two operations were performed using high potassium cold cardioplegic solution. Six of these eight patients had direct implantation of the ostium of the left coronary artery into the aorta, one had a saphenous vein bypass graft from the aorta to the left coronary artery and one had only ligation of the left coronary artery at its origin. Only two of these eight patients survived the operation. One of the two survivors had the benefit of high potassium cold cardioplegia and the other did not.

Each of these eight patients had cardiomegaly demonstrated by an anteroposterior chest roentgenogram. The cardiothoracic ratio ranged from 68 to 84 percent (average 74).

In seven of the eight patients an electrocardiogram was available for analysis. The electrocardiograms were performed at an average age of 3.7 months. Four of these seven patients had unequivocal electrocardiographic evidence of myocardial infarction and three did not. Of the two patients who survived operation, one had electrocardiographic evidence of myocardial infarction and the other did not.

All eight patients had cardiac catheterization and most had elevated left ventricular end-diastolic pressure ranging from 10 to 28 mm Hg (average 16). Peak systolic pulmonary arterial pressure ranged from 24 to 42 mm Hg (average 35). Peak systolic left ventricular pressure ranged from 70 to 100 mm Hg (average 85). The ratio of peak systolic pulmonary to left ventricular pressure

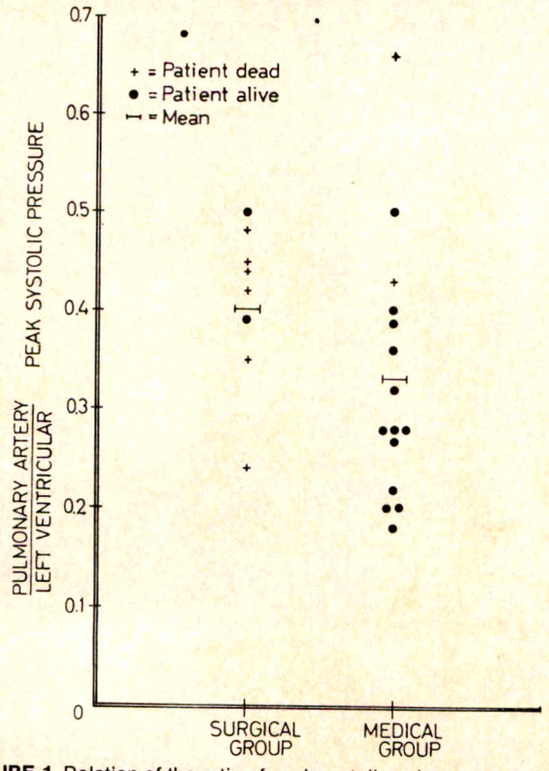

FIGURE 1. Relation of the ratio of peak systolic pulmonary arterial to left ventricular pressure to medical or surgical treatment in 23 infants.

anged from 0.24 to 0.50 (average 0.40) (Fig. 1). A reliible left ventricular ejection fraction could be determined from the left ventricular angiogram in seven of ight patients. The ejection fraction was depressed in ll and ranged from 9.2 to 24 percent (average 17). All ight patients had a dominant right coronary arterial ystem, and all had angiographic evidence of a left to ight shunt through the anomalous coronary artery. The atio of systemic to pulmonary blood flow ranged from .84 to 1.2 (average 1.05).

Seven of the eight patients had an M mode echocardiogram (Table II). The left ventricular shortening fraction was decreased in all patients, ranging from 3 to 28 percent (average 15). The ratio of left atrial to aortic root dimension ranged from 1.1 to 1.8 (average 1.5). The left ventricular end-diastolic dimension was increased in all seven patients and ranged from 3.4 to 6.5 standard deviations above the normal mean (average 4.6). All seven patients had a hypokinetic posterior ventricular wall, and two of these seven also had a hypokinetic septum.

Of the two patients who survived the operation, one has now survived 4 months and the other 4 years since operation. The cardiothoracic ratio of the latter patient has decreased from 84 percent preoperatively to 64 percent at present.

Medical Group

Operation was delayed until after 1 year of age in 15 of the 23 patients (Table III). Thirteen of these 15 patients are alive and 2 have died. The two deaths occurred at ages 16 and 17 months, respectively, and neither child had an operation. The present age of the 13 survivors ranges from 7 to 28 years (average 13.7). Of the 13 patients who survived, 9 have had an operation at an age ranging from 1.2 to 12.8 years (average 7.6). Only two of the nine operations were performed using high potassium cold cardioplegic solution. Of the nine patients who underwent operation, three had direct implantation of the left coronary ostium to the aorta, three had a saphenous vein bypass, two a left coronary arterial ligation and one a left subclavian to coronary arterial bypass. None of these patients died. Four of the 13 surviving patients have not had operative intervention; their ages range from 2 to 9 years (average 7.6).

We could determine the cardiothoracic ratio from a chest roentgenogram in 11 of these 15 medically treated patients. In the remaining four patients we either could not locate a chest roentgenogram or the quality of the roentgenogram was such that a reliable cardiothoracic ratio could not be determined. The cardiothoracic ratio for these 11 patients ranged from 52

ABLE II

chocardiographic Features: Surgical Group

Case	Outcome	Age at Echocardiography (mo)	Weight (kg)	Shortening Fraction (%)	LA/AO	Left Ventricular End-Diastolic Dimension		Hypokinesia	
						Absolute (mm)	+SD	Septum	PLVW
S-1	D	2	4	13	2	38	6.5	0	+
S-2	S	2.5	4.5	12	1.1	33	4.4	0	+
S-3	S	4	6.2	14	1.5	35	4.2	+	+
S-4	D	4	4	18	1.1	28	3.4	0	+
S-5	D	6	5.9	28	1.8	36	4.6	0	+
S-6	D	2	4.4	6	1.3	36	5.7	0	+
S-8	D	3	5.4	3	1.7	31	3.4	+	+
Average	. . .	3.4	4.9	13.4	1.5	33.8	4.6	. . .	. . .

D = died; LA/AO = ratio of left atrial to left ventricular dimension; PLVW = posterior left ventricular wall; S = survived; +SD = standard deviations ove the mean.

TABLE III

Medical Group

Case	Outcome	ECG MI	ECG Age (mo)	Cardiothoracic Ratio (%)	Cardiac Catheterization Age (mo)	LVEDP (mm Hg)	LVEF (%)	Qp/Qs	Peak Systolic Pressure (mm Hg) PA	LV	PA/LV	Operation Age (mo)	Type	PO (mo)
M-1	S	0	5	...	144	0	59	1.0	23	115	0.20	154	SV	124
M-2	D	0	10	78*	10*	...	10*	0.97*	50*	75*	0.66*	...	...	...
M-3	S	+	1	...	14	5	31	1.17	22	80	0.28	14	L	199
M-4	S	0	60	52	72	8	42	1.09	24	120	0.20	...	...	...
M-5	S	...	...	...	7*	...	15*	1.16*	28*	100*	0.28*	48	I	60
M-6	D	0	11	70*	11	20*	12*	1.13*	34*	80*	0.43*	...	...	...
M-7	S	0	2	72*	2*	8*	68*	1.04*	30*	75*	0.40*	...	...	...
M-8	S	+	42	58	45	8	...	1.09	20	90	0.22	93	I	41
M-9	S	+	6	63	10*	19*	...	1.03*	45*	90*	0.50*	...	...	...
M-10	S	+	4	68	139	...	...	1.13	36	92	0.39	89	SV	116
M-11	S	+	66	76	2*	8*	...	1.14*	24*	90*	0.27*	96	L	117
M-12	S	0	12	68	1*	10*	55*	0.92*	32*	90*	0.36*	...	...	...
M-13	S	+	168	55	144	...	...	1.90	20	110	0.18	135	SV	161
M-14	S	+	4	71	4*	15*	...	1.0*	32*	100	0.32	126	I	33
M-15	S	+	12	...	60	8	...	1.0	25	90	0.28	72	SC	122
Average†	...	...	28.7	6.4	44.3	10.6	36.5	1.05	29.6	93	0.33	91.8	...	108
Average‡	...	...	...	71.1*	5.8*	14.4	32*	1.04*	34.4*	87.5*	0.40*	...	...	...

* Less than 12 months of age. † Of all studies. ‡ Of studies at less than age 12 months.
SC = subclavian arterial to left coronary arterial anastomosis; other abbreviations as in Table I.

to 78 percent (average 66). Chest roentgenography in seven of these patients was performed in the 1st year of life (comparable with that in the surgical group), and the cardiothoracic ratio in these patients ranged from 63 to 78 percent (average 71).

Fourteen of the 15 patients had an electrocardiogram available for analysis. Electrocardiography was performed at an average age of 28.7 months. Eight of the 14 patients had unequivocal evidence of myocardial infarction, whereas 6 had no electrocardiographic evidence of infarction. Neither of the 2 patients who died had electrocardiographic evidence of myocardial infarction.

All 15 patients had cardiac catheterization at an age ranging from 2 months to 12 years. Reliable records of left ventricular end-diastolic pressure were obtained from 11 patients, and the pressure ranged from 5 to 20 mm Hg (average 10.6). Eight patients had catheterization at less than 1 year of age (comparable with the age in the surgical group), and in five of these patients left ventricular end-diastolic pressure ranged from 8 to 20 mm Hg (average 14.4). Peak systolic pulmonary arterial pressure ranged from 20 to 50 mm Hg (average 29.6). Peak systolic left ventricular pressure ranged from 75 to 120 mm Hg (average 90). The ratio of peak systolic pulmonary to left ventricular pressure ranged from 0.18 to 0.66 (average 0.33). In eight patients who had cardiac catheterization at less than 1 year of age, peak systolic pulmonary arterial pressure averaged 34.4 mm Hg, peak systolic left ventricular pressure averaged 87.5 mm Hg and the ratio averaged 0.40 (Fig. 1). A reliable left ventricular ejection fraction could be determined from the left ventricular angiogram in 8 of the 15 patients and ranged from 12 to 68 percent (average 36.5). In five of these patients catheterization was performed at less than 1 year of age (comparable with the age in the surgical group), and the ejection fraction ranged from 12 to 68 percent (average 31.8). All 15 patients had a dominant right coronary arterial system and all had angiographic evidence of a left to right shunt through the anomalous left coronary artery. The ratio of systemic to pulmonary blood flow ranged from 0.90 to 1.16 (average 1.05).

Six of the 15 patients underwent M mode echocardiography at an age ranging from 9 months to 7 years (Table IV). The left ventricular shortening fraction ranged from 6 to 33 percent (average 26.7). The ratio of the left atrial and aortic dimension ranged from 1.1 to 1.6 (average 1.4). The left ventricular end-diastolic dimension ranged from 1.4 to 4.9 standard deviations above the normal mean (average 2.7). Left ventricular hypokinesia was noted in only 1 patient, who died during medical treatment.

Infant Subset

Ten of the 23 patients had cardiac catheterization with a documented left ventricular ejection fraction of less than 20 percent in the first 11 months of life. This subset of patients tended to have more severe symptoms of congestive heart failure and a greater cardiothoracic ratio on chest roentgenography than did patients with an ejection fraction greater than 20 percent. Seven of these patients were treated surgically and 2 are alive (28 percent survival rate). The five deaths occurred in the immediate postoperative period at ages 2, 2, 4, 5 and 9 months, respectively. Of the two survivors, one has had a reduction in cardiac size with a decrease in the cardiothoracic ratio from 84 to 64 percent. The other patient is early in the follow-up period. Both patients continue to require digitalis and diuretic therapy. Three of the 10 patients were treated medically and 1 is alive (33 percent survival rate). The two deaths occurred at

TABLE IV

Echocardiographic Features: Medical Group

Case	Outcome	Age at Echocardiography (mo)	Weight (kg)	Shortening Fraction (%)	LA/AO	Left Ventricular End-Diastolic Dimension		Hypokinesia	
						Absolute (mm)	+SD	Septum	PLVW
M-2	D	10	5.9	6	1.5	32	3.2	+	+
M-4	S	60	15.4	28	1.6	40	2.1	0	0
M-7	S	48	15.5	32	1.1	38	1.8	0	0
M-8	S	84	26	29	1.1	47	3.0	0	0
M-9	S	36	15	28	1.5	36	1.4	0	0
M-12	S	9	7.9	33	1.7	40	4.9	0	0
Average	...	41	14.3	26	1.4	38.8	2.7	...	...

Abbreviations as in Table II.

16 and 14 months of age, respectively. The one survivor has had spontaneous improvement of the left ventricular ejection fraction from 15 percent at age 8 months to 33 percent at age 48 months. At age 5 years, after myocardial revascularization at age 48 1/2 months, she has a left ventricular ejection fraction of 57 percent.

Discussion

Natural history and prognosis: There is considerable disagreement concerning the optimal management of symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery. Some investigators[5–11] suggest that surgical intervention either to ligate the left coronary artery or to establish prograde flow through this artery is indicated as soon as the diagnosis is established. This aggressive surgical approach stems, in part, from the previously reported poor prognosis for patients with this anomaly. Wesselhoeft et al.[2] reported a 93 percent mortality rate for infants with this anomaly in whom symptoms developed between 2 and 4 months of age. Perry and Scott[13] reported on 11 infants with anomalous origin of the left coronary artery from the pulmonary artery in whom symptoms of congestive heart failure developed at age 3 weeks to 4 months. Only 2 of these 11 patients survived (82 percent mortality rate). Four of their patients were treated surgically and three died (75 percent mortality rate); of the seven treated medically, six died (85 percent mortality rate).

However, the frequent assumption that symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery have an invariably poor prognosis may be incorrect. Perry and Scott[13] reviewed 4 previously reported cases of anomalous origin of the left coronary artery from the pulmonary artery and found a mortality rate of only 32 percent. Arciniegas et al.[5] reported an overall mortality rate of 34 percent. A previous study from this center reported a 20 percent mortality rate in 10 patients with anomalous origin of the left coronary artery from the pulmonary artery. Indeed, the two deaths occurred after ligation of the left coronary artery. The overall mortality rate for symptomatic infants with this anomaly in the present study is 34 percent. Indeed, on the basis of our study and previous studies,[3,10,11] the overall mortality rate for symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery is between 30 and 35 percent.

How can one reconcile the disparate reports of the natural history of this cardiac malformation? As with most diseases, there is a selection process so that the sickest patients come to medical attention earlier than less severely affected patients. Also, some patients are misdiagnosed as having endocardial fibroelastosis, myocarditis or idiopathic congestive cardiomyopathy and are discovered only later in life to have anomalous origin of the left coronary artery from the pulmonary artery. In some published studies patient records are sought through hospital files as well as autopsy files. These factors tend to select the sickest patients with the disease and will bias the mortality data and the reported natural history. It is important to recognize this bias because an understanding of the natural history of the disease is critical in making any reasonable decision concerning the effect of therapy.

Subset of patients with poor prognosis during 1st year of life: In this study the patients operated on at less than 1 year of age appear to have been sicker than those treated medically. Although all patients in both the medical and the surgical groups were symptomatic, the surgical group had cardiac catheterization at an earlier age, had a higher left ventricular end-diastolic pressure, a higher peak systolic pulmonary pressure and ratio of peak systolic pulmonary to left ventricular pressure and a lower left ventricular ejection fraction than did the medical group. Thus it appears that selecting the sickest patients for operation in this study creates a bias against the operative results. However, when one examines the outcome of patients with a left ventricular ejection fraction of 20 percent of less, both medical (33 percent survival rate) and surgical (28 percent survival rate) modes of therapy have similar survival results. This finding suggests that there is a subset of patients with anomalous origin of the left coronary artery from the pulmonary artery and very poor left ventricular function who will have a very high mortality rate in the 1st year of life regardless of therapy. However, there is a large group of patients with a

left ventricular ejection fraction greater than 20 percent who will survive without early surgical intervention and who should be spared the risk of operation in the 1st year of life.

Role of left ventricular function in surgical decision: Although surgery in the 1st year of life is no better and perhaps worse than medical management in promoting survival, does early surgical myocardial revascularization decrease the progression of left ventricular fibrosis and preserve or improve myocardial function? The answer is unclear. Levitsky et al.[6] reported on a 10 month old child who had direct implantation of the left coronary artery into the aorta. Seven months postoperatively this patient had improved left ventricular function. The left ventricular ejection fraction increased from 30 to 48 percent, end-diastolic pressure decreased from 10 to 7 mm Hg, and the first derivative of left ventricular pressure (dP/dT) increased from 400 to 1,375 mm/s. One of our two survivors of early surgical intervention had a reduction of the cardiothoracic ratio on chest roentgenography from 84 percent at age 2 months to 64 percent at age 21 months. For the other survivor it is still too early in the postoperative period to be able to judge the effect. However, we have seen improvement of left ventricular function with medical therapy only. Patient M-5 had a left ventricular ejection fraction of 15 percent at age 8 months, and at age 48 months it was 33 percent without operative myocardial revascularization. Ihenacho et al.[17] also reported spontaneous improvement in a patient with anomalous origin of the left coronary artery from the pulmonary artery.

Recently Arciniegas et al.[5] reported the outcome of 23 patients with anomalous origin of the left coronary artery from the pulmonary artery treated in their institution. Six of 23 infants died between 2 and 8 months of age without surgical intervention. Seventeen patients were treated by a variety of operative techniques (ligation of the left coronary artery, 4 patients; implantation of the left coronary artery into the aorta, 1 patient; saphenous vein bypass graft, 7 patients; and subclavian to coronary arterial bypass graft, 5 patients), and 2 of these 17 patients died. These investigators concluded that reestablishment of a two coronary arterial system is the procedure of choice, especially in infancy. We must disagree with their conclusion. Both their study and the present study reviewed the course of 23 patients, and in both studies 8 patients died. However, in one study early surgical intervention is advocated, while in the other medical therapy with delayed surgical intervention is advocated. These disparate conclusions are probably a result of the difference in the selection of the medical and surgical groups in the two studies. While we tended to select the sickest patients for early surgical intervention, the Arciniegas report[5] suggests that they elected not to operate on the youngest, sickest patients. The different conclusions of those two studies highlight the possibility that there are two subsets of symptomatic infants with anomalous origin of the left coronary artery from the pulmonary artery. One subset includes very sick infants with a markedly decreased left ventricular function who have a mortality rate of approximately 70 percent regardless of the mode of therapy. The other subset will do well regardless of the mode of therapy with essentially no mortality. It is important that the patients in the latter subset not be subjected to the risk of early surgical intervention but be managed by medical means until they reach an age and size when an operation has minimal risk.

Role of magnitude of left to right shunt and pulmonary hypertension: Other investigators have suggested that the magnitude of the left to right shunt and the degree of pulmonary hypertension predict outcome and can be used as a guideline for surgical or medical therapy. Perry and Scott[13] reviewed 44 cases and classified the patients into three groups: (1) those with sufficient intercoronary anastomosis to be associated with an increase in oxygen saturation in the pulmonary artery, (2) those with intercoronary anastomosis insufficient to produce an increase in oxygen saturation in the pulmonary artery but with a left to right shunt at the level of the pulmonary artery detectable by dye dilution curves or by cineangiography, and (3) those with no detectable evidence of a left to right shunt in the pulmonary artery or pulmonary hypertension, or both. Askenazi and Nadas[14] recommend that infants with a "sizable" left to right shunt be treated conservatively until attaining an age and size suitable for coronary arterial bypass. If only a small left to right shunt is demonstrable, these investigators recommend surgical intervention because the prognosis with conservative therapy is poor.

In our study, we could demonstrate no relation between the magnitude of the left to right shunt and outcome with either early surgical or medical therapy. The ratio of systemic to pulmonary blood flow was 1.05 in both the medically and the surgically treated patients. Although the ratio of systemic to pulmonary blood flow in the patients who died (Qp/Qs ratio = 1.03) was slightly smaller than in those who survived (Qp/Qs ratio = 1.06), this difference was not statistically significant. There was a relation between the ratio of peak systolic pulmonary arterial and left ventricular pressure and outcome. The average ratio of peak systolic pulmonary arterial to left ventricular pressure was 0.43 for the patients who died and 0.32 for those who survived. Also, the ratio of peak systolic pulmonary arterial to left ventricular pressure was greater in the patients operated on (0.40) than in those treated medically (0.33). An increased ratio of peak systolic pulmonary artery to left ventricular pressure probably reflects reduced left ventricular function and associated mitral regurgitation and is an index of the severity of disease. Indeed, it supports the contention that we selected sicker patients for operative intervention than we selected for medical therapy.

Recommendation for patient management: Our present recommendations for the management of symptomatic infants with anomalous origin of the left

coronary artery from the pulmonary artery are as follows: (1) Treat patients with evidence of recent myocardial infarction according to the principles of modern coronary care. These include rest and administration of oxygen, morphine when indicated, digitalis, diuretic drugs and appropriate antiarrhythmic agents.[14] (2) Continue appropriate doses of digitalis and diuretic drugs for the patients with congestive heart failure but without recent acute myocardial infarction. Afterload-reducing agents may be beneficial in some of these patients, but this is unproved in infants. (3) Delay operative revascularization until patients are at least 18 months of age and in many cases until 5 to 7 years of age. At the time of operation attempt to establish a two coronary system rather than perform simple ligation of the left coronary artery. The risk of surgical intervention in the 1st year of life is prohibitively high.

Acknowledgment

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Coronary Artery Disease in the Hurler Syndrome

Qualitative and Quantitative Analysis of the Extent of Coronary Narrowing at Necropsy in Six Children

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The amount of cross-sectional area luminal narrowing in each 5 mm segment of each of the four major epicardial coronary arteries (right, left main, left anterior descending and left circumflex) is described at necropsy in six children (aged 3 to 16 years) with the Hurler syndrome. In five patients at least one of the four major coronary arteries was narrowed 76 to 100 percent, and in four of these five patients all four major arteries were narrowed to this extent. Of the 24 major coronary arteries in the six patients, 17 (71 percent) were narrowed 76 to 100 percent at some point. A total of 182 segments were examined from the 24 major coronary arteries, and the extent of narrowing was as follows: 96 to 100 percent, 14 (8 percent); 76 to 95 percent, 61 (34 percent); 51 to 75 percent, 59 (32 percent); 26 to 50 percent, 39 (21 percent) and 0 to 25 percent, 9 (5 percent). By applying a score of 1 to 4 to each 5 mm segment according to its category of narrowing (1 = 0 to 25 percent; 2 = 26 to 50 percent; 3 = 51 to 75 percent and 4 = 76 to 100 percent), the 182 segments had a total score of 570 and a mean score of 3.2, indicating that each segment was narrowed an average of about 67 percent in cross-sectional area. Thus, narrowing of the major epicardial coronary arteries at necropsy is usually diffuse and severe in the Hurler syndrome, which is the cause of the most severe coronary narrowing in childhood.

Patients with the Hurler syndrome (dwarfism, severe mental retardation skeletal malformations, hepatosplenomegaly and corneal opacities) are known to have a variety of cardiovascular lesions that affect the coronary arteries, cardiac valves, mural endocardium, myocardial walls and aorta.[1–6] Within the affected cardiac structures are large clear cells (known as Hurler cells), granular cells, acid mucopolysaccharide materia and collagen.[6] Although it is well known that the epicardial coronary arteries may be narrowed in the Hurler syndrome,[6] the extent of the narrowing has not been described. To fill this void, each of the four major epicardial coronary arteries in six patients with the Hurler syndrome was examined in a quantitative manner at necropsy, and the results of that examination are described in this report.

Methods

Study patients: During life, none of the six patients with the Hurler syndrom had symptoms of cardiac dysfunction or evidence of myocardial ischemia. Specifically, none had dyspnea, evidence of chest pain or overt signs of congestive cardiac failure. Three had precordial murmurs (grade 2/6, apical, systolic), and three had cardiomegaly on chest radiography. Electrocardiograms were available for all but one patient (Case 1): in four, they were recorded during the last 2 weeks of life, and in the remaining patient (Case 3), 8 years before death. None of the five had electrocardiographic evidence of myocardial ischemia. All five had sinus tachycardia, two patients (Cases 3 and 5) had right axis deviation and right atrial abnormality, one patient (Case 6) had low voltage and one (Case 5) had occasional premature ventricular beats. None had unequivocal evidence of either right or left ventricular hypertrophy.

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At necropsy, each had diffuse thickening of all four cardiac valves and of ventricular mural endocardium, and three had calcific deposits in mitral anuli. All six also had Hurler cells in the interstitium between some myocardial cells. One patient had a small focus of subendocardial fibrosis. Atherosclerotic plaque in the aorta was impressive. These noncoronary cardiovascular findings in five of the six patients are described in detail elsewhere.[6]

Coronary arterial examination: Grossly, the right, left main, left anterior descending and left circumflex coronary arteries (hereafter called the four major coronary arteries) were firm and the amount of surrounding subepicardial adipose tissue was minimal (Fig. 1). The coronary arteries were examined as follows: Each was excised intact, fixed and cut transversely to its longitudinal axis into segments approximately 5 mm long, and each segment was labeled sequentially from either its aortic ostium or from its origin from the left main artery. The 5 mm segments were labeled, dehydrated (alcohol and xylene) and embedded in paraffin, and two histologic sections were cut and stained from each paraffin block. Movat stain was used on one histologic section, and all determinations of luminal narrowing were based on examination of the Movat-stained sections. The degrees of luminal narrowing were based on histologic examination of each cross section magnified 25 to 50 times.

The judgment regarding the degree of luminal narrowing of each 5 mm segment was based on the degree of luminal obliteration within the luminal circle bordered by the internal elastic membrane. The circle was visually subdivided into four equal-sized quadrants, and the extent of cross-sectional area luminal narrowing in each 5 mm segment was classified as follows: 0 to 25, 26 to 50, 51 to 75 or 76 to 100 percent. The latter category was subdivided into 76 to 95 and 96 to 100 percent to determine the number of segments totally occluded or nearly so. The accuracy of these judgments by visual inspection under microscopy has been shown by comparison with video planimetry to have a rate of error of less than 5 percent.[7]

Results

Of the 24 total major epicardial coronary arteries in the six patients with the Hurler syndrome, 17 (71 percent) were narrowed 76 to 100 percent in cross-sectional area at some point, an average of 2.8 coronary arteries per patient. In four patients all four major coronary arteries were narrowed 76 to 100 percent in cross-sectional area; in one patient (Case 3) only one of the four arteries and in another (Case 6) none of the four arteries was severely narrowed. In four of the six patients, the left main coronary artery was severely narrowed (76 to 100 percent).

Quantitative analysis of coronary segments: The results of the quantitative analysis of the 5 mm long coronary segments from each of the four major coronary arteries in each of the six study patients are summarized in Figure 2 and Table I, and the amounts of narrowing in each of the four major arteries in the six patients are summarized in Figure 3. Of the 182 coronary segments examined in the six patients, 14 (8 percent) were narrowed 96 to 100 percent in cross-sectional area; 61 (34 percent) 76 to 95 percent; 59 (32 percent) 51 to 75 percent; 39 (21 percent) 26 to 50 percent; and 9 (5 percent) to 25 percent. Although the overall amount of narrowing was extensive, there was considerable variation among the six patients. The most severe narrowing occurred in Patients 4 and 5, who were brothers: all 47 of their coronary segments (100 percent) were narrowed 76 to 100 percent in cross-sectional area, including 11 segments (23 percent) narrowed 96 to 100 percent. In Patient 2, 58 percent of the segments were narrowed 76 to 100 percent, and in Patient 1 (the youngest, age 3 years), 26 percent were so narrowed. In contrast, in Patient 3 only 1 (3 percent) of 37 segments was severely narrowed (76 to 100 percent), and in Patient 6 (the oldest of the six patients, age 16 years), none of the 32 segments was severely narrowed.

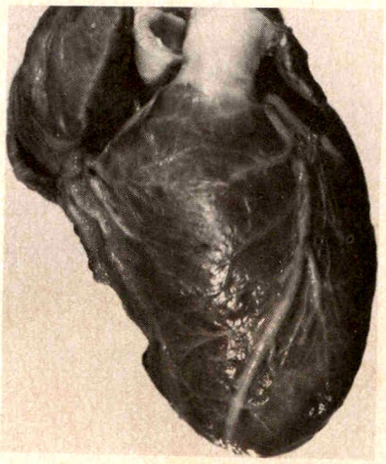


FIGURE 1. Patient 5. Epicardial surface of the heart. The left anterior descending coronary artery is far more prominent than expected for an 11 year old boy (A70-236) because of the artery's firmness (from the intraluminal deposits of Hurler cells, granular cells, collagen and acid mucopolysaccharide material), and the expected adjacent subepicardial adipose tissues are absent.

The extent of the coronary narrowing in each of the six patients and in the six patients as a whole also can be readily appreciated by applying a numerical score to the amount of cross-sectional area narrowing in each 5 mm coronary segment, as follows: narrowing 0 to 25 percent = 1; 26 to 50 percent = 2; 51 to 75 percent = 3; and 76 to 100 percent = 4 (Table I). Of the 182 segments, the total score was 570 and the mean score 3.2. Thus, each of the 5 mm segments was narrowed an average of about 67 percent in cross-sectional area, and the mean scores in the six patients ranged from 2.2 (Patient 3) to 4 (the highest possible score, found in the two brothers, Patients 4 and 5). The percent of coronary segments classified in each of the five categories of narrowing was similar in all four major coronary arteries (Fig. 3).

Histologic analysis: The coronary luminal narrowing in all six patients and in all 182 coronary segments was produced primarily by a combination of Hurler cells, granular cells, collagen and acid mucopolysaccharide material (Fig. 4). In only one patient (Case 5) were lipid deposits, namely, foam cells and a few extracellular lipid accumulations, found in the coronary arteries. Only one patient (also Patient 5) had calcific

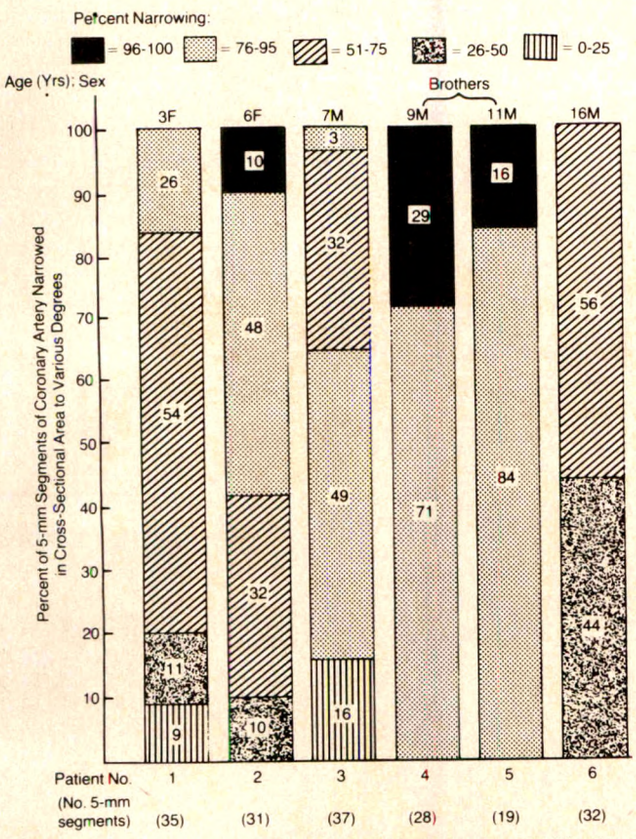


FIGURE 2. Bar graph showing the percent of 5 mm segments of the four major coronary arteries in five categories of narrowing in each of the six patients with the Hurler syndrome.

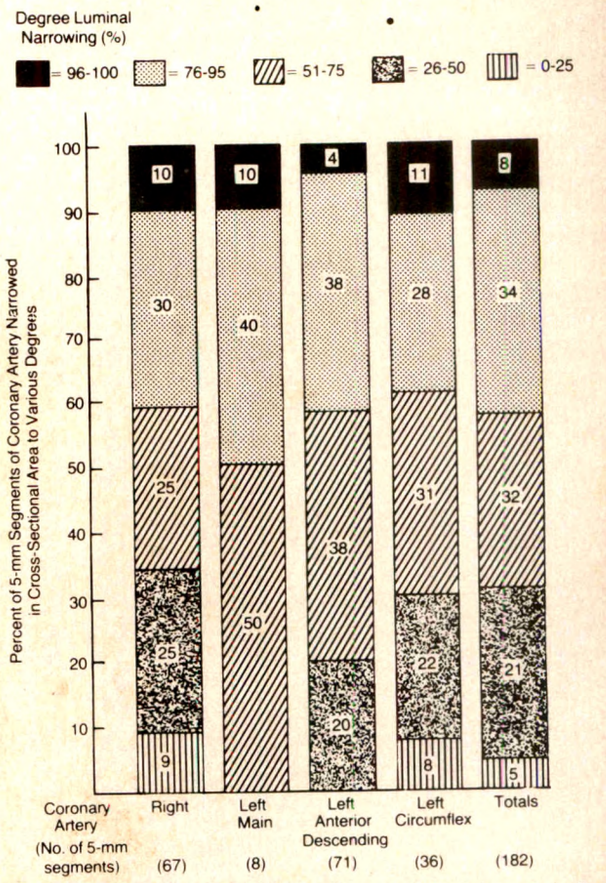


FIGURE 3. Bar graph showing the percent of 5 mm segments in five categories of narrowing in each of the four major epicardial coronary arteries in the six patients.

deposits, but these were present in only 1 of 19 segments.

Comments

Coronary artery disease in Hurler's syndrome: This necropsy study indicates that patients with the Hurler syndrome usually have diffuse and severe coronary luminal narrowing produced primarily by a combination of Hurler cells, fibrous tissue and acid mucopolysaccharide material. The presence of the Hurler cells indicates the specific cause of the luminal narrowing. The amount of coronary luminal narrowing was severe (76 to 100 percent) in five of the six patients, and in all six it was far more extensive than expected in the first 2 decades of life. Of the 24 coronary arteries studied in the six patients, 17 (71 percent) were narrowed 76 to 100 percent in cross-sectional area, and in

TABLE I

Number, Total Score and Mean Score of the 5 mm Segments of the Four Major Epicardial Coronary Arteries Narrowed to Various Degrees in Each Patient

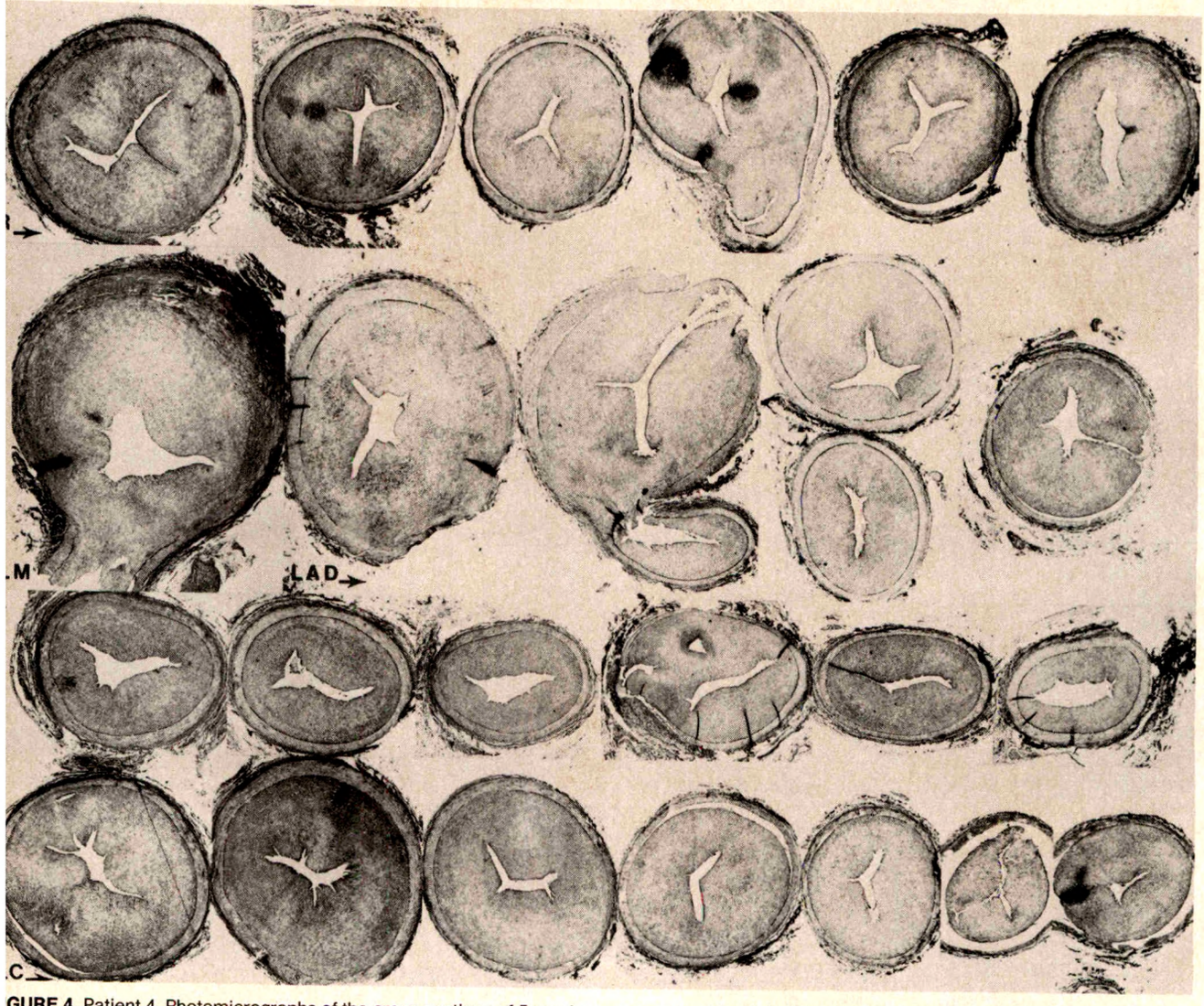
Case	5 mm Coronary Segments With Various Degrees of Narrowing in XSA (n)				Total 5 mm Segments	Score	
	0–25%	26–50%	51–75%	76–100%		Total*	Mean†
1	3	4	19	9	35	104	3.0
2	0	3	10	18	31	108	3.5
3	6	18	12	1	37	82	2.2
4	0	0	0	28	28	118	4.0
5	0	0	0	19	19	76	4.0
6	0	14	18	0	32	82	2.6
Total	9 (5%)	39 (21%)	59 (32%)	75 (42%)	182 (100%)	570	3.2

* Sum derived by assigning a number to each segment in each of the four categories of cross-sectional area (XSA) narrowing as follows: 1 = 0 to 25 percent narrowing; 2 = 26 to 50 percent; 3 = 51 to 75 percent; and 4 = 76 to 100 percent.

† Number derived by dividing the total number of 5 mm coronary segments per patient into the total score per patient.

four patients all four major coronary arteries, including the left main, were narrowed to this degree. Analysis of the degrees of narrowing of each 5 mm long segment of each of the four coronary arteries from each of the six patients disclosed that 75 (42 percent) of the 182 segments were narrowed 76 to 100 percent in cross-sectional area, including 14 (8 percent) that were narrowed 96 to 100 percent. Of the total group of 182 coronary segments, 134 (73 percent) were narrowed greater than 50 percent in cross-sectional area. To emphasize further the diffuse extent of the coronary narrowing, only 9 (5 percent) of the 182 coronary segments were narrowed 25 percent or less in cross-sectional area. The extent of the coronary narrowing is especially noteworthy in view of the young age of the patients (mean age 9 years, range 3 to 16) and the absence of clinical evidence of myocardial ischemia in all six patients or necropsy evidence of left ventricular fibrosis or necrosis in five of the six patients. The Hurler syndrome appears to be the cause of the most severe coronary narrowing in the first 2 decades of life.

Comparison with arteriosclerotic coronary disease: The extent and severity of the coronary narrowing in our six patients with the Hurler syndrome are similar to those observed at necropsy in adults with fatal coronary heart disease. Of 116 adult patients with fatal coronary atherosclerosis studied in our laboratory by an identical quantitative approach, the percent of 5 mm coronary segments narrowed 76 to 100 percent in cross-sectional area by atherosclerotic plaque in various groups of patients was as follows: sudden coronary death, 36 percent[8]; acute transmural myocardial infarction, 34 percent[9]; unstable angina pectoris, 47 percent[10]; healed myocardial infarction with chronic, eventually fatal congestive cardiac failure, 29 percent[11] and healed myocardial infarction with asymptomatic course after healing of the acute infarction and noncardiac death, 32 percent.[12] Thus, the extent of the se-



GURE 4. Patient 4. Photomicrographs of the cross sections of 5 mm long segments of the right (R), left main (LM), left anterior descending (LAD) ıd left circumflex (LC) coronary arteries in a 9 year old boy (A66-199) with the Hurler syndrome. The residual lumens are more or less centrally cated.

vere coronary narrowing in our patients with the Hurler syndrome was identical to that in our necropsy patients with unstable angina pectoris, which was the largest subset of adult patients with coronary disease. In contrast, however, to the 116 patients with coronary atherosclerosis, all of whom had clinical evidence of myocardial ischemia, none of our patients with the Hurler syndrome had such evidence even though nearly 50 percent of the lengths of their major coronary arteries was 76 to 100 percent narrowed in cross-sectional area, and only 1 of these patients had a left ventricular scar, and it was small and subendocardial.

In addition to the unique composition of the luminal material in our patients with the Hurler syndrome, the location of the residual lumens was quite different from that observed in patients with atherosclerotic coronary disease. In all of the latter patients, the lumens of the narrowed coronary arteries were eccentrically located at some point so that some portions of the arterial lining were not covered by atherosclerotic plaque. In our patients with the Hurler syndrome, the lumen in every 5 mm segment of coronary artery was centrally located or nearly so, and all portions of the arterial lining were covered by the Hurler-type plaque.

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Two Dimensional Echocardiographic Evaluation of Mustard Operation for d-Transposition of the Great Arteries

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Two dimensional sector scan echocardiography was used to evaluate the morphologic characteristics of the surgically revised atria in 17 patients with d-transposition of the great arteries who had undergone the Mustard operation. Echocardiographic imaging of the atria was obtained from various planar projections. Dimensional measurements of various segments of the systemic and pulmonary venous atria were obtained in each patient. Correlative hemodynamic, angiographic, postmortem and echocardiographic data showed that seven patients (Group I) had no structural abnormalities of the atria. These 7 patients served as controls for 10 other patients with structural abnormalities of the surgically created atria. One patient (Group II) showed stenosis of the junction of the superior vena cava and systemic venous atrium compared with findings in the control group. Three patients (Group III) had significantly reduced echocardiographic dimensions of the junction of the anterior and posterior segments of the pulmonary venous atrium. Six patients (Group IV) had increased echocardiographic dimensions of all components of the pulmonary venous atrium due to tricuspid regurgitation. These data show that qualitative and quantitative two dimensional sector echocardiography can reliably detect structural abnormalities of the surgically revised atria after the Mustard operation.

Echocardiography has proved an important method for diagnosing d-transposition of the great arteries[1] and provides qualitative and quantitative assessment of associated lesions.[2,3] Indirect echographic criteria for estimating hemodynamic variables such as pulmonary arterial[4,5] and left ventricular pressures[6] are being developed. Two dimensional echocardiography has significantly improved the ability to diagnose not only transposed great vessels but also associated lesions.[7–9] Direct inspection of the interatrial[8] and interventricular septum,[9] the left ventricular outflow tract,[9] the pulmonary arteries and their first branches,[7] ventricular chamber size and atrioventricular (A-V) alignment[9] can be made in real time motion.

After the Mustard operation the intraatrial baffle can be detected with M mode echocardiography, and quantitation of the newly created systemic and pulmonary venous atria has been reported.[10–12] However, only limited and relatively undefined segments of these atria are visualized on M mode echocardiography, and abnormalities such as superior and inferior vena caval or pulmonary venous atrial stenosis cannot be diagnosed.[13] The purpose of this study was to evaluate with sector scan echocardiography the morphologic characteristics of the pulmonary and systemic venous atria and the A-V valves in patients with d-transposition of the great arteries who had had the Mustard operation. Correlative angiographic and pathologic findings indicate that two dimensional echocardiography is capable of detecting abnormalities of these structures.

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Methods

Study patients: Seventeen patients, aged 4 months to 17 years, with d-transposition of the great arteries who had undergone the Mustard operation are included in this study. Seven patients (Group I) had no hemodynamic, angiographic or echocardiographic evidence of atrial chamber abnormalities after the Mustard operation and were considered to have had an ideal repair (Table I). These seven patients were retrospectively selected to serve as control subjects matched for body surface area to the 10 patients with structural abnormalities of the atria after the Mustard procedure (Table II). One patient (Group II) had both superior vena caval and pulmonary venous atrial obstruction, three patients (Group III) had stenosis of the pulmonary venous atrium, and six (Group IV) had tricuspid regurgitation.

Echocardiography: All patients had hemodynamic and angiographic evaluation by cardiac catheterization (Tables III and IV). The echocardiographic examination was performed with the patient in the supine position and the examiner seated to the right. A phased array real time sector scanner (Varian Associates model 3000, 2.25 megahertz transducer) or a mechanical sector scanner (ATL model 315A) was employed. The images were recorded from several planar projections.[13,14] The direction of the transducer and echocardiographic sector beam movements (right, left, anterior, posterior and so on) are described with reference to the patient's body.

Sector imaging of the systemic venous atrium: Descriptively the systemic venous atrium was divided into superior and inferior vena caval segments and their respective isthmic connections to the main body of the systemic venous atrium (Fig. 1A). The transducer was placed at the suprasternal notch location with the sector beam oriented in the coronal plane of the body, and images of the aorta and the right pulmonary artery were initially obtained. The transducer

TABLE I

Two Dimensional Echocardiographic Quantification of Atrial Segments in Seven Patients Without Structural Abnormalities of the Atria After the Mustard Operation (Group I)

Patients	BSA (cm^2)	PVA Dimensions (cm)			SVA Dimensions (cm)		
		Post	Isth	Ant	SVC_S	SVC_I	IVC_S
1	1.27	2.4	1.4	2.3	1.7	1.2	1.6
2	1.20	NR	NR	NR	1.4	0.9	1.6
3	1.28	1.6	1.4	2.2	1.0	0.9	2.1
4	0.60	1.5	1.5	1.9	1.0	0.6	0.9
5	0.94	1.9	1.4	2.1	0.9	0.7	0.9
6	0.90	2.1	1.7	2.2	NR	NR	NR
7	0.33	1.5	0.9	1.2	0.8	0.6	0.8
Mean	0.93	1.83	1.38	1.98	1.13	0.82	1.32
SD	0.36	0.37	0.26	0.41	0.34	0.23	0.53

Ant = anterior pulmonary venous atrial segment; BSA = body surface area; Isth = isthmic pulmonary venous atrial segment; IVC_S = inferior vena caval segment of the systemic venous atrium; NR = not recorded; Post = posterior pulmonary venous atrial segment; PVA = pulmonary venous atrium; SD = standard deviation; SVA = systemic venous atrium; SVC_I = isthmic segment of the systemic venous atrium; SVC_S = superior vena caval segment of the systemic venous atrium.

TABLE II

Two Dimensional Echocardiographic Quantification of Atrial Segments in 10 Patients With Structural Abnormalities of the Atria After the Mustard Operation (Groups II to IV)

Patients	BSA (cm^2)	PVA Dimensions (cm)			SAV Dimensions (cm)		
		Post	Isth	Ant	SVC_S	SVC_I	IVC_S
			Group II				
8	0.33	1.5	0.9	1.9	1.2	0.3	0.7
			Group III				
9	0.98	2.4	0.9	2.3	1.7	1.3	1.4
10	0.78	1.7	1.0	2.4	1.1	1.0	1.4
11	1.02	2.1	0.8	2.4	1.0	1.0	1.2
Mean	0.93	2.1	0.9	2.4	1.3	1.1	1.3
SD	0.13	0.35	0.1	0.06	0.38	0.17	0.12
			Group IV				
12	0.76	4.1	4.1	4.1	1.5	1.5	1.5
13	0.95	3.4	3.8	3.8	1.3	1.3	NR
14	1.60	4.3	4.3	4.3	1.8	1.2	1.9
15	1.50	5.0	5.0	5.0	NR	1.1	2.2
16	0.33	1.9	2.3	2.3	1.0	0.7	1.6
17	0.90	2.6	2.6	3.4	1.5	1.6	1.6
Mean	1.00	3.6	3.7	3.8	1.42	1.2	1.8
SD	0.48	1.15	1.0	0.9	0.29	0.32	0.29

Abbreviations as in Table I.

was then tilted anteriorly and the superior vena caval segment and the segment of the isthmus connecting it to the main systemic venous atrial chamber were visualized. Occasionally the inferior vena caval segment of the systemic venous atrium could also be imaged from this transducer location and sector beam plane (Fig. 1B). Quantitation of the various segments of the systemic venous atrium was done at peak systole. The diameters at various levels were measured at right angles to the approximate long axis of each segment, and an average of three to four measurements was obtained at each level.

The inferior vena cava and inferior vena caval segments of the systemic venous atrium could be well visualized from

TABLE III

Hemodynamic Data on Seven Patients Without Structural Abnormalities of the Atria After the Mustard Operation (Group I)

Patients	Age at Op (yr)	Age at Cath (yr)	BSA at Cath (cm^2)	Age at Echo (yr)	Associated Lesion Postop	Pressures (mm Hg) RVP S/D	PAP S/D (mean)	PVA_p a/v (mean)	PVA_a a/v (mean)	PA_w a/v (mean)	Δ LVO	SVC a/v (mean)	SVA a/v (mean)
1	5.0	7.0	1.2	9.0	None	110/10	18/8 (13)	NR	10/16 (6)	8/14 (8)	8	7/9 (7)	7/8 (6)
2	1.0	7.5	1.2	7.6	None	100/5	16/8 (11)	4.5/6.5 (11)	5/6 (5)	5/6.5 (5.5)	10	3.5/6 (4)	1.5/7 (3)
3	2.0	6.0	1.2	10.0	LVOS, dynamic; atrial shunt Qp/Qs 1.6/1	110/7	28/10 (18)	NR	9/24 (18)	14/22 (17)	28	8/11 (8.5)	17/12 (9)
4	1.3	3.3	0.6	3.3	LVOS, dynamic	105/8	20/6 (10)	NR	8/14 (8)	8/12 (7)	26	6.5/9 (6.5)	6.5/9 (6.5)
5	1.5	6.0	0.9	8.0	LVOS, dynamic	100/5	24/8 (16)	NR	8/9 (7)	8/10 (9)	18	5/7 (6)	4/6 (4)
6	2.0	8.0	0.9	8.7	Subaortic stenosis, small VSD, mild AI	130/5	20/8 (12)	NR	(4)	6/7 (5)	4	7/7 (4)	4/5 (2)
7	2 days	0.58	0.33	0.7	PAH, PVD	105/9	70/30 (45)	NR	9/22 (14)	18/22 (17)	0	7.5/9 (7.5)	7.5/7.5 (6)

AI = aortic insufficiency; a/v = *a* wave/*v* wave; BSA = body surface area; Cath = catheterization; ΔLVO = peak systolic pressure difference between the left ventricle and the pulmonary artery; Echo = echocardiography; LVOS = left ventricular outflow stenosis; NR = not recorded; Op = operation; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PA_w = pulmonary arterial wedge pressure; Postop = after Mustard operation; PVA_a = anterior segment of the pulmonary venous atrium; PVA_p = posterior segment of the pulmonary venous atrium; PVD = pulmonary vascular disease; Qp/Qs = pulmonary to systemic flow ratio; RVP = right ventricular pressure; S/D = systolic/diastolic; Subao = subaortic; SVA = systemic venous atrium; SVC = superior vena cava; VSD = ventricular septal defect.

TABLE IV

Hemodynamic Data on 10 Patients With Structural Abnormalities of the Atria After the Mustard Operation

Patients	Age at Op (yr)	Age at Cath (yr)	BSA at Cath (cm^2)	Age at Echo (yr)	Associated Lesion Postop	Pressures (mm Hg) RVP S/D	PAP S/D (mean)	PVA_p a/v (mean)	PVA_a a/v (mean)	PA_w a/v (mean)	Δ LVO	SVC a/v (mean)	SVA a/v (mean)
						Group II							
8	0.3	2.3	0.33	2.3	Small VSD, PDA	95/9	35/12 (22)	NR	10/30 (12)	13/15 (11)	0	15/19 (14.5)	10/9 (5)
9	2.2	4.0	0.57	11.0	LVOS dynamic	90/8	24/14 (17)	NR	8/20 (14)	NR	10	4/6 (4)	4/6 (4)
10	1.0	4.0	0.61	9.0	LVOS dynamic	75/4	24/12 (16)	NR	8/16 (10)	14/17 (14)	36	4/7 (5.5)	5/7 (5.5)
11	1.3	6.0	0.77	10.0	LVOS dynamic	90/4	30/14 (19)	NR	2/12 (4)	14/6 (13)	25	5/8 (5)	5.5/7.5 (5)
						Group IV							
12	2.1	3.3	0.63	5.0	VSD	120/11	24/10 (17)	NR	12/20 (13)	10/20 (13)	43	9/11 (8.5)	8/11 (8)
13	9.0	10.0	0.95	9.0	VSD	90/7	25/8 (20)	NR	10/14 (8)	12/16 (9)	70	7/9 (7)	8/10 (6)
14	16.4	17.0	1.60	16.5	Dextrocardia, VSD, SMTV	100/20	98/45 (60)	28/60 (28)	NR	35/40 (30)	0	20/20 (19)	23/23 (19)
15	7.0	16.0	1.45	16.0	VSD	100/16	60/30 (42)	16/16 (26)	NR	28/28 (21)	0	16/16 (14)	16/14 (14)
16	0.7	1.3	0.33	1.3	LVOS, IVS	80/15	40/20 (25)	NR	14/28 (14)	24/28 (17)	8	9/11 (8)	10/11 (7)
17	8.0	8.7	0.90	8.6	LVOS, VSD, SMTV	90/12	40/12 (24)	12/42 (18)	10/50 (20)	16/32 (17)	30	9/10 (7)	9/10 (7)

IVS = intact ventricular septum; PDA = patent ductus arteriosus; SMTV = septal malattachment of tricuspid valve; other abbreviations as in Table III.

the subxiphoid location with the sector beam oriented in the sagittal plane (Fig. 1C). A rightward angulation and clockwise rotation of the sector beam with additional anterosuperior angulation was utilized to view the superior vena caval segments. The right border of the cardiac silhouette in this view was formed by the pulmonary venous atrium.

The superior vena caval segment could also be viewed from the subxiphoid location (Fig. 2). The imaging search was initiated by directing the sector beam in a horizontal (four chamber) plane. Anterosuperior angulation of the transducer beam imaged the pulmonary artery with its first branches arising from the left ventricle (Fig. 3B), and a rightward and further anterior angulation confirmed the position of the anterior aorta arising from the right ventricle. Continued rightward direction of the echocardiographic beam brought into view the superior vena caval segment and the isthmic segment to the systemic venous atrium. In this image view the pulmonary venous atrium lay rightward and inferior to these structures (Fig. 2).

The systemic venous atrium could also be viewed in the left ventricular long axis view obtained from the left parasternal transducer location (fourth to fifth intercostal space). The pulmonary artery and left ventricle were visualized first in the left ventricular long axis view. The isthmic segment of the systemic venous atrium was seen behind the pulmonary artery, and with superior and rightward angulation of the echocardiographic sector beam the superior vena caval segment of the systemic venous atrium could be visualized. At times the transducer had to be shifted to the lower left parasternal location (fifth to sixth intercostal space) to obtain this view.

In a short axis view from the left parasternal transducer location at the base of the heart (Fig. 4), the superior vena caval-isthmic segment of the systemic venous atrium was imaged behind the pulmonary artery and left ventricular outflow. The pulmonary venous atrium was well visualized and seen to be composed of a posterior segment with pulmonary veins and an anterior segment close to the tricuspid valve.

Imaging of the pulmonary venous atrium: An echocardiographic image obtained from the apical transducer location with the echocardiographic sector beam oriented in a horizontal (four chamber) plane was most useful for evaluating the pulmonary venous atrium. After the Mustard operation the pulmonary venous atrium is divided into a posterior segment adjacent to the pulmonary veins, an anterior segment adjacent to the tricuspid valve and an isthmus representing the junction between the anterior and posterior segments (Fig. 5 A and B). The isthmus was bounded medially by the intraatrial baffle and laterally by the free wall of the surgically created pulmonary venous atrium (Fig. 5C). These segments were measured at peak systole using the transverse diameters at right angles to the approximate long axis of each segment. An average of the three to four such measurements from different cardiac cycles was used (Fig. 5C).

The pulmonary venous atrium could also be evaluated from the subxiphoid transducer location using the four chamber view. The anterior and posterior orientation of the respective segments could be well seen (Fig. 6, D and E). The parasternal short axis view also delineates the anatomy of the pulmonary venous atrium as a transverse section close to the pulmonary artery and left ventricular outflow (Fig. 4).

Because the diagnosis of tricuspid insufficiency was suggested in some cases from the increased echocardiographic dimensions of the pulmonary venous atrium and because the morphologic substratum for tricuspid insufficiency in transposition of the great arteries has not been reported in detail,

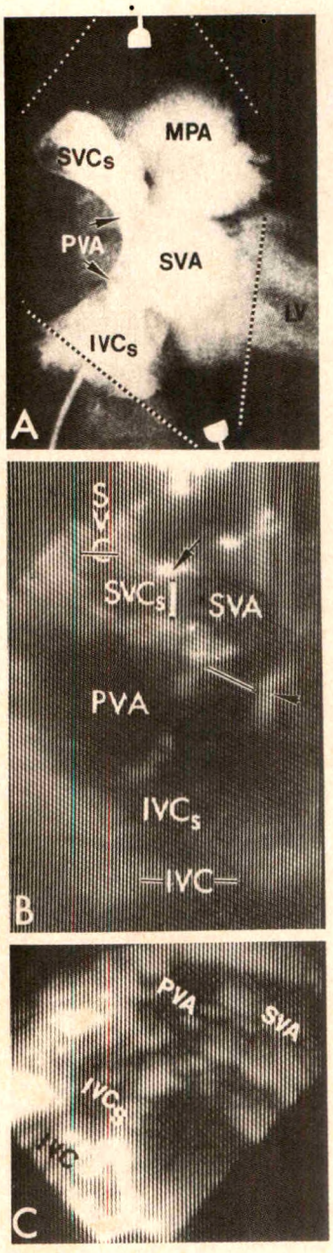

FIGURE 1. Case 16. Transposition of the great vessels and intact ventricular septum after Mustard operation. **A,** angiocardiogram of the systemic venous atrium (SVA), anteroposterior view. The systemic venous atrium is divided for descriptive purposes into superior (SVCs) and inferior vena caval segments (IVCs) with their connecting portions, termed the isthmus (**arrows**), joining them to the main body of the systemic venous atrium. The pulmonary venous atrium (PVA) lies to the right of the systemic venous atrium and forms the right border of the cardiac silhouette. **B,** sector scan, suprasternal view, with sector beam in the coronal body plane. The superior vena cava (SVC), the superior vena caval segment of the systemic venous atrium, the connecting isthmus (**upper arrow**) and the main body of the systemic venous atrium are well visualized. The inferior vena caval segment and its isthmus (**lower arrow**) are unusually well visualized in this patient. The pulmonary venous atrium forms the right border of the cardiac silhouette. **Bars** indicate the position of dimensional measurements of these segments which are made approximately at right angles to the long axis of each segment. **C,** the inferior vena caval segment and isthmus are best visualized from the subxiphoid transducer position with the sector beam in the sagittal body plane and tilted superiorly in a rightward direction. MPA = main pulmonary artery.

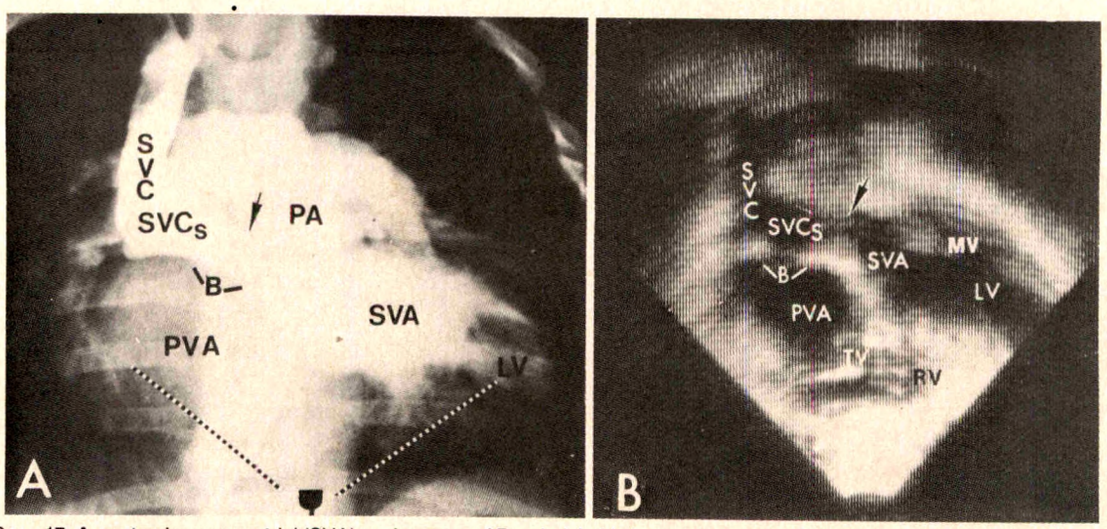

FIGURE 2. Case 17. **A,** systemic venous atrial (SVA) angiogram and **B,** subxiphoid view sector scan with sector beam directed rightward and slightly anteriorly. The superior vena caval segment (SVCs) and isthmus (**arrow**) can also be imaged from this sector projection. The position of the superior vena caval segment portion of the intraatrial baffle (B) separating the segment from the surgically created pulmonary venous atrium (PVA) is well defined. LV = left ventricle; MV = mitral valve; PA = pulmonary artery; RV = right ventricle; SVC = superior vena cava; TV = tricuspid valve.

an autopsy study of the tricuspid valve was made in 50 hearts with complete d-transposition, 20 hearts with an intact ventricular septum, 20 hearts with a ventricular septal defect and 10 hearts with left ventricular outflow stenosis with or without a ventricular septal defect.

Validation of findings: Validation of the two dimensional echocardiographic scan structure identification in this study was achieved by (1) correlating the angiographic and echocardiographic appearances of these atria in each patient, (2) performing echocardiographic contrast studies during cardiac catheterization, in one patient with injection of indocyanine green into the systemic venous and pulmonary venous atria (Fig. 6), and (3) performing pathologic, echocardiographic and angiographic correlations in two patients (Fig. 7).

Results

Group I: The sector scans of patients with an ideal repair (Group I) showed that the dimension of the superior vena caval-isthmic segment of the systemic venous atrium was narrower (0.82 ± 0.23 cm) than that of the superior vena caval segment (1.13 ± (0.34 cm) (Table I). These patients showed no significant (2 mm Hg or less) pressure gradient at either the superior or inferior vena caval junction with the systemic venous atrium. The inferior vena caval segment measurement was the largest of the various systemic venous atrial segments when quantitated with the subxiphoid scan (1.32 ± 0.53 cm).

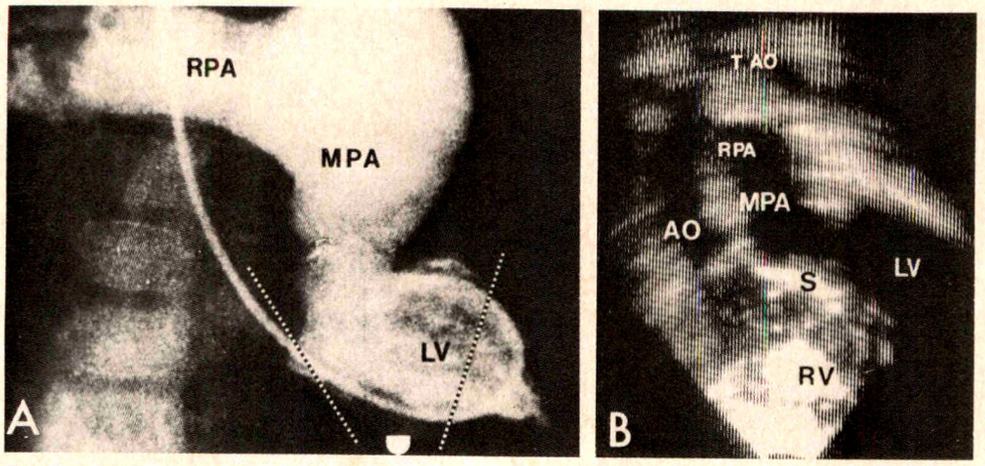

FIGURE 3. Case 9. **A,** left ventricular angiogram and **B,** subxiphoid view sector scan. Imaging of the superior vena caval segment of the systemic venous atrium is begun by obtaining a four chamber image and orienting the sector beam in the horizontal plane. With superior and anterior tilting of the echographic beam, the origin of the pulmonary artery (MPA) from the left ventricle (LV) and its branches can be defined. In this patient, the origin of the aorta (AO) from the right ventricle (RV) is unusually well visualized. Further anterior and rightward beam angulation from this position shows the superior vena caval segments and the systemic venous atrium (Fig. 2B). RPA = right pulmonary artery; S = interventricular septum; TAO = transverse aorta.

In Group I the dimensions of the anterior segments of the pulmonary venous atrium (1.98 ± 0.40 cm) were slightly larger than those of the posterior (1.83 ± 0.37 cm) or isthmic segments (1.38 ± 0.26 cm) (Table I). The isthmus was the narrowest segment, with the narrowing caused by rightward and ventral bulging of the intraatrial baffle. Angiographically, a mild waist in the pulmonary venous atrium was noted at this site; however, no pressure gradient was recorded at the isthmus in any of these patients.

Group II: Only one patient (Group II, Case 8) showed angiographic and hemodynamic evidence of stenosis of the superior vena caval-isthmic segment. The appearance of the suprasternal and subxiphoid sector scans correlated well with the angiographic appearance (Fig. 8). The dimension of the isthmus was markedly smaller (0.3 cm) than that of the superior vena caval segment (1.2 cm), and at cardiac catheterization there was a mean pressure difference of 9 mm Hg across the isthmus between the superior vena cava and the systemic venous atrium.

Group III: In Groups III and IV the superior vena caval-isthmic segment was slightly narrower than superior or inferior vena caval segments, similar to findings in the group with ideal repair (Group I), and none of these patients showed an abnormally large pressure difference across the isthmus.

In three patients (Group III), mild to moderate abnormal narrowing of the isthmic portion of the pulmonary venous atrium was noted both angiographically and echocardiographically (Fig. 9). In these three patients a mid diastolic murmur was audible at the mid and lower right sternal border and was considered to originate from within the narrowed pulmonary venous atrial isthmus. In Group I patients no such murmur was present. Sector scan measurements of the pulmonary venous atrial segments in these three patients showed significant narrowing of the isthmic portion (1.0 cm or less) (Table II). Hemodynamic studies in these patients performed a few years earlier than the echographic study demonstrated mild to moderate elevation of pulmonary arterial wedge pressure which, in the absence of ostial stenosis of the pulmonary veins, reflects the pressure of the posterior segment of the pulmonary venous atrium (Table IV). The degree of obstruction of the pulmonary venous atrium was not considered sufficient to require additional surgery in any of these patients.

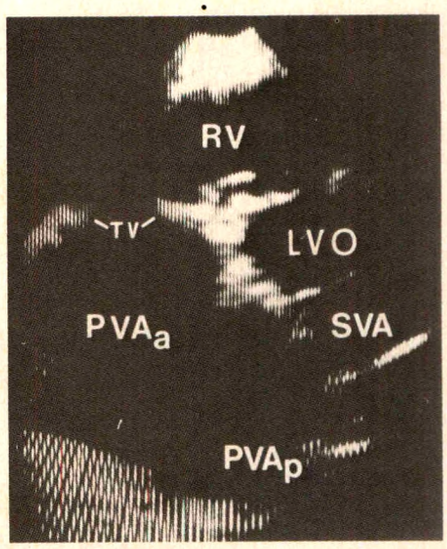

FIGURE 4. Case 15. Two dimensional sector scan, short axis view, recorded from the base of the heart at the parasternal location. A small segment of the systemic venous atrium (SVA) is seen behind the left ventricular outflow tract (LVO). The posterior (PVA_p) and anterior segments (PVA_a) of the pulmonary venous atrium are imaged in this view. RV = right ventricle; TV = tricuspid valve.

Group IV: Tricuspid regurgitation (Group IV) was established on the basis of hemodynamic and angiographic evidence in six patients. The sector scan dimensions of all segments of the pulmonary venous atrium in this group were increased and the mild isthmic narrowing noted in the control patients (Group I) was not present (Table II). In two of these patients prominent systolic pulsation of the pulmonary venous atrium

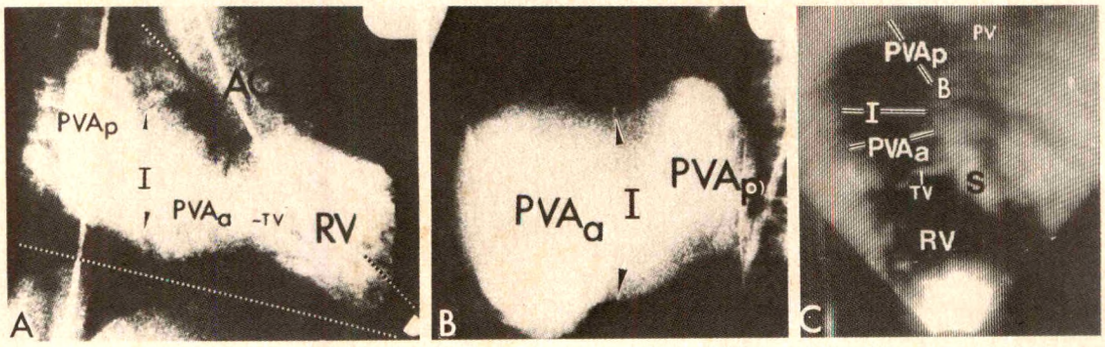

FIGURE 5. Case 12. **A**, right ventricular (RV) angiogram, anteroposterior view; **B**, pulmonary venous angiogram, lateral view; and **C**, foreshortened apical view sector scan of a patient with tricuspid regurgitation. The pulmonary venous atrium (PVA) is divided into a posterior segment (PVA_p) adjacent to the pulmonary veins and an anterior segment (PVA_a) adjacent to the tricuspid valve (TV) with a connecting isthmic portion (I). Pulmonary veins (PV) and the convex bulge of the intraatrial baffle (B) are well visualized in **C**. **Bars** indicate the site of transverse diameter measurements of these segments. AO = aorta; RV = right ventricle; S = interventricular septum.

was noted extending back posteriorly as far as the pulmonary veins. The angiographic and echocardiographic images of the pulmonary venous atrium were easily correlated (Fig. 10).

Preoperatively, five patients had a ventricular septal defect, two had subpulmonary stenosis and one patient had an intact ventricular septum with subpulmonary stenosis. Clinically, a pansystolic murmur was noted at the lower left sternal and xiphoid areas with accentuation in intensity during inspiration. Moderate to marked cardiac enlargement was evident in chest roentgenograms. Compared with findings in the normal control patients, right ventricular end-diastolic pressure was increased (Table IV). Right ventricular angiograms showed moderate to severe tricuspid insufficiency, and a dilated pulmonary venous atrium was noted in all. In order to achieve a satisfactory patch closure of the ventricular septal defect, the tricuspid valve was detached and subsequently reattached to the rim of the ventricular septal defect in three patients. One of the six patients with tricuspid insufficiency had an intact ventricular septum; the insufficiency was secondary to severe right ventricular dysfunction (angiographic ejection fraction 27 percent). On two dimensional sector scans in five patients, the tricuspid valve closure was abnormally horizontal (Fig. 10 top, B) in contrast to normal oblique tricuspid valve apposition. No definite systolic separation of the leaflets could be observed. In the sixth patient, the septal leaflet of the tricuspid valve was immobile because of its incorporation within the patch used to close the ventricular septal defect.

Postmortem study of the tricuspid valve: Additional postmortem study of the tricuspid valve in complete transposition with or without operative intervention revealed the following: Of the 20 heart specimens without ventricular septal defect, 7 (35 per-

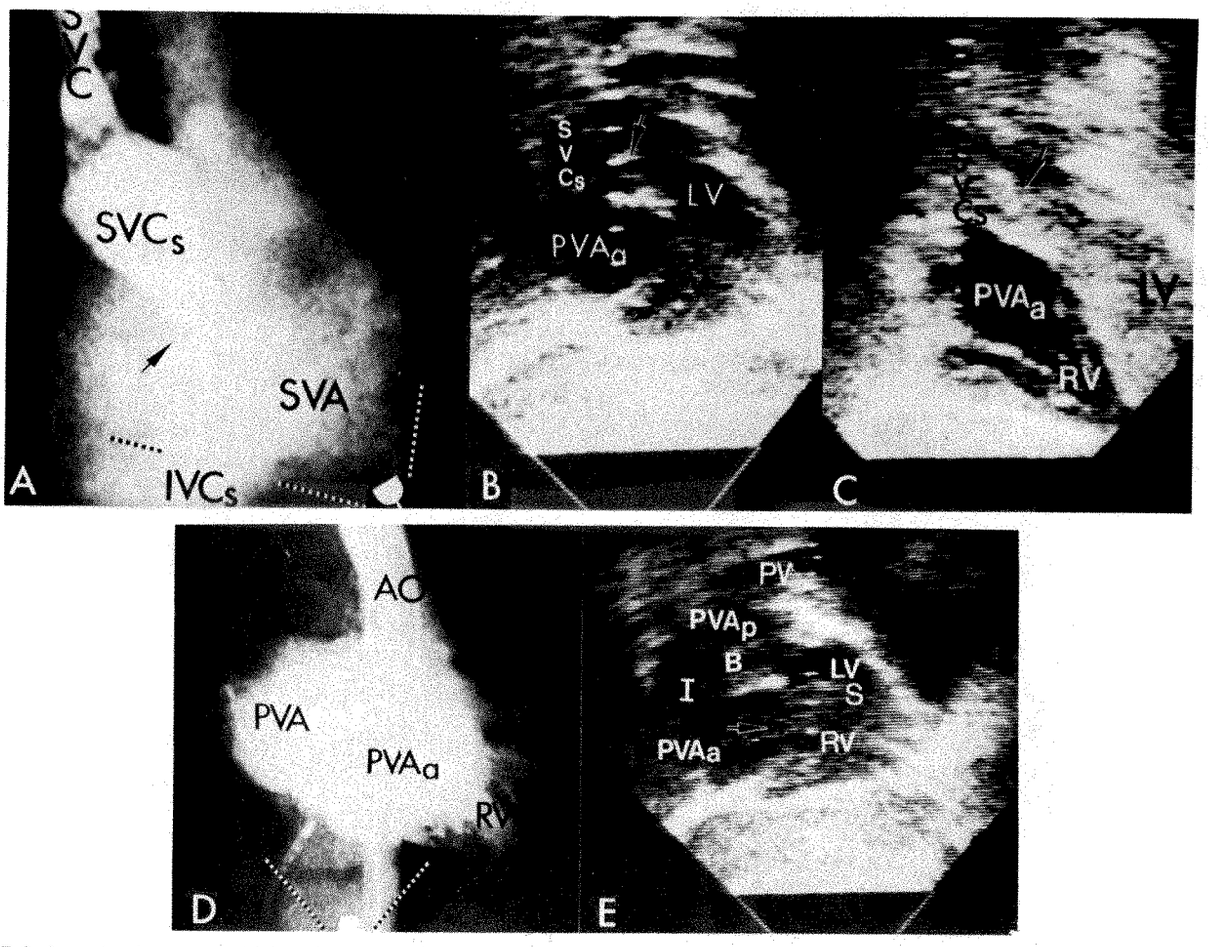

FIGURE 6. A, systemic venous atrial angiogram, anteroposterior view, and **B**, subxiphoid sector scan view of the superior vena caval segment SVCs) recorded during cardiac catheterization in an additional patient not included in the study. **A**, slight narrowing of the isthmus is noted (**arrow**); **3**, a faint catheter image is also noted within the isthmus. **C**, injection of indocyanine green in the superior vena cava opacifies the superior vena caval segment and the left ventricle (LV) and confirms the identification of these structures. **D**, pulmonary venous atrial (PVA) angiogram, anteroposterior view, and **E**, subxiphoid sector echocardiogram (four chamber view). Injection of indocyanine green into the right ventricle (RV) shows regurgitation of echocardiographic contrast material into the dilated anterior segment of the pulmonary venous atrium (**arrow**) and confirms the identity of these structures. Abbreviations as in Figure 5.

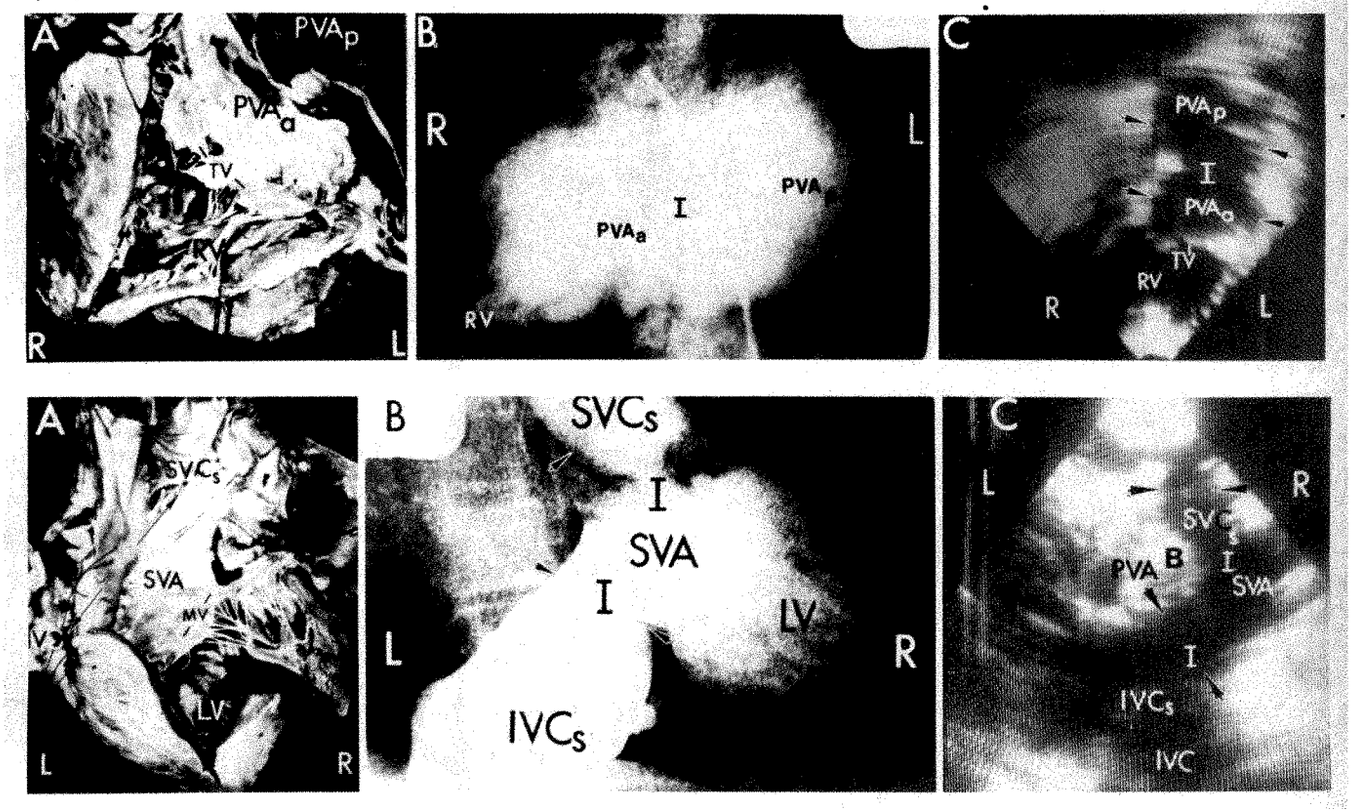

FIGURE 7. Case 14. **Top panel. A,** postmortem heart specimen; **B,** pulmonary venous angiogram (anteroposterior view); and **C,** sector scan, apical view, correlating the morphologic features of the pulmonary venous atrium with transposition of the great arteries and mirror-image dextrocardia. Severe tricuspid insufficiency developed after the Mustard operation due to a tricuspid valve leaflet disruption by the ventricular septal defect patch closure. All segments of the pulmonary venous atrium (PVA) and the isthmus (I) are grossly enlarged. Malapposition of the tricuspid valve (TV) can be seen on the sector scan. **Bottom panel. A,** postmortem heart specimen; **B,** systemic venous angiogram; and **C,** sector scan, suprasternal view with echocardiographic beam in the coronal body plane correlating the morphologic features of the systemic venous atrium. Because the systemic venous atrium (SVA) in the pathologic specimen is viewed from the posterior aspect, the correlative angiogram and echogram are reversed for laterality matching. **Arrows** in **B** and **C** indicate some of the sites used for dimensional measurements. B = intraatrial baffle; L = left; R = right; other abbreviations as in Figures 1 and 4.

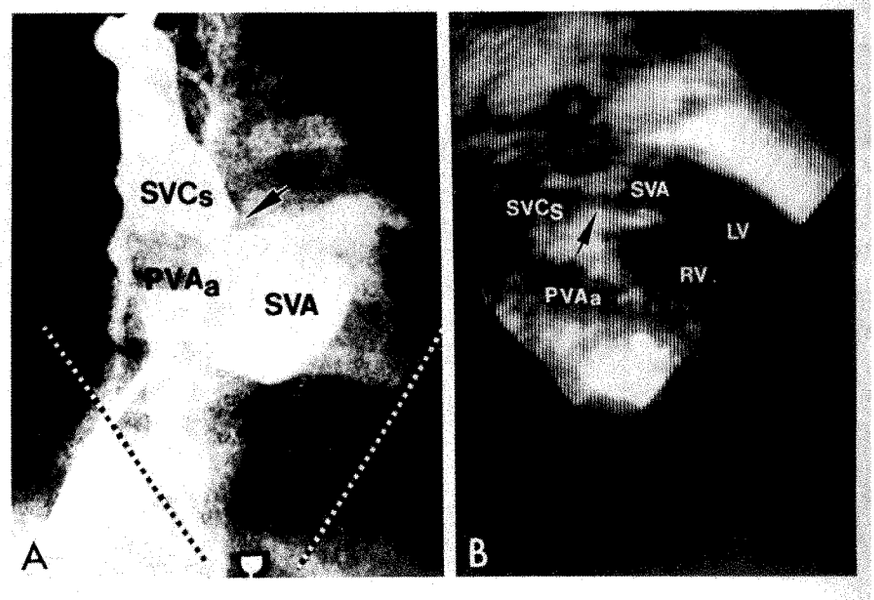

FIGURE 8. Case 7. **A,** systemic venous atrial angiogram and **B,** subxiphoid view sector scan illustrating severe stenosis of the superior vena caval segment (SVCs) isthmus (**arrows**). Abbreviations as in Figures 1 and 4.

cent) had anatomic abnormalities of the tricuspid valve; of 20 heart specimens with ventricular septal defect, 12 (60 percent) had abnormalities; and of 10 hearts with left ventricular outflow tract stenosis with or without ventricular septal defect, 4 (40 percent) had abnormalities of the tricuspid valve. Certain abnormalities were common to all three groups. The medial leaflet was attached by papillary muscles either to the septum or the septal band. The medial and inferior leaflets were often not sharply demarcated from each other, being more or less one leaflet (mitralization). Occasionally, the medial and anterior leaflets were fused. The anterior leaflet was sometimes divided into two leaflets. In one patient with a ventricular septal defect, tricuspid insufficiency was attributed to abnormal plastering of the medial portion of the anterior tricuspid leaflet against the ventricular septum. All tricuspid valves showed increased hemodynamic change.[15]

The autopsy patient with marked tricuspid insufficiency diagnosed with echocardiography (Fig. 7) had mirror-image dextrocardia with a large ventricular septal defect and previous Mustard operation. At autopsy the tricuspid orifice was enlarged. Each leaflet was divided into two parts, and there were two papillary muscles for each of the medial and inferior leaflets.

Discussion

Detection of stenosis and dilatation of the aorta: Our study shows that two dimensional echocardiography can be used to assess qualitatively and quantitatively the morphologic characteristics of the newly created systemic and pulmonary venous atria in patients with transposition of the great arteries after the Mustard operation. Although quantitation of anatomically bizarrely shaped atria may be subject to interobserver variability, this approach has prospectively helped us to detect stenosis and pathologic dilatation of these atria. The site and severity of these abnormalities was shown to correlate accurately with the angiographic appearances. Longitudinal follow-up may then be particularly facilitated by this noninvasive means so that progression of the lesions can be assessed during growth.

Only one patient in our study showed superior vena caval obstruction at the superior vena caval-isthmic junction,[16–18] which is the most likely site of stenosis in the systemic venous atrium. The slightly increased pressure in the superior vena cava did not necessitate revision of the atrial repair. We have not encountered an example of inferior vena caval-isthmic stenosis to date.

Stenosis of the pulmonary venous atrium[19–21] *was noted in three patients,* and was hemodynamically mild in one and moderate in two. The site of the stenosis was the isthmus between the posterior and anterior segments where the intraatrial baffle with its anterior and ventral bulge usually makes a waist in the pulmonary venous atrium. This seems to be the usual area of narrowing, and various surgical techniques have been used to enlarge the pulmonary venous atrium at this site by

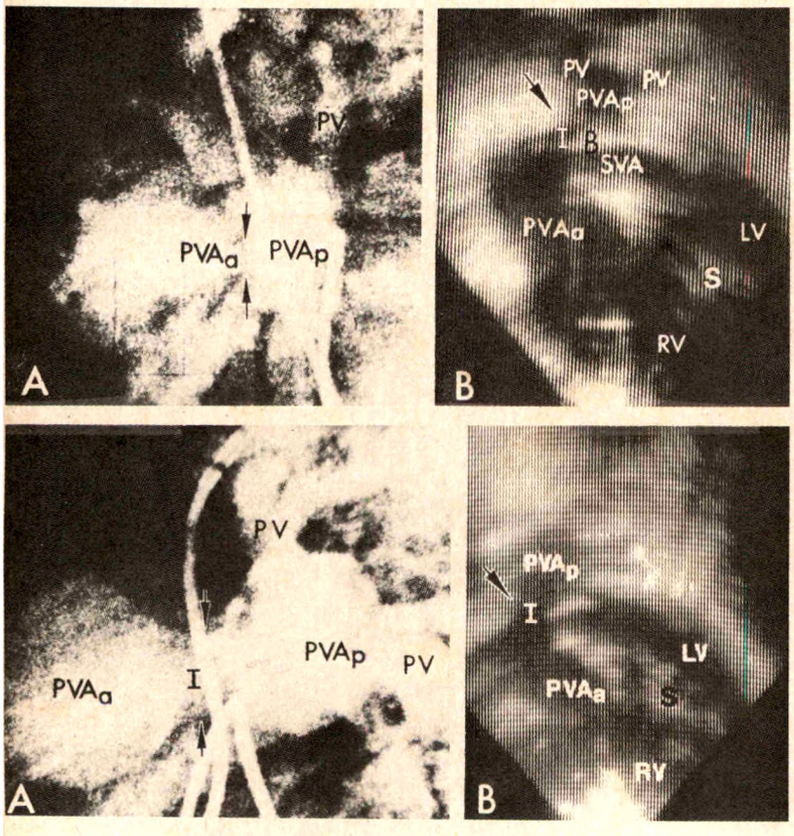

FIGURE 9. Top panel, Case 11. **A**, pulmonary venous atrial (PVA) angiogram, lateral view; and **B**, sector scan, apical view. Moderately severe stenosis (**arrows**) of the isthmus (I) is shown, giving the pulmonary venous atrium an hourglass appearance. The pulmonary veins (PV) are clearly viewed in the sector scan and are unobstructed. **Bottom panel,** Case 9. **A**, angiogram, lateral view, and **B**, sector scan, apical view, illustrating a lesser degree of isthmic stenosis of the pulmonary venous atrium (**arrows**). Abbreviations as in Figures 1 and 4.

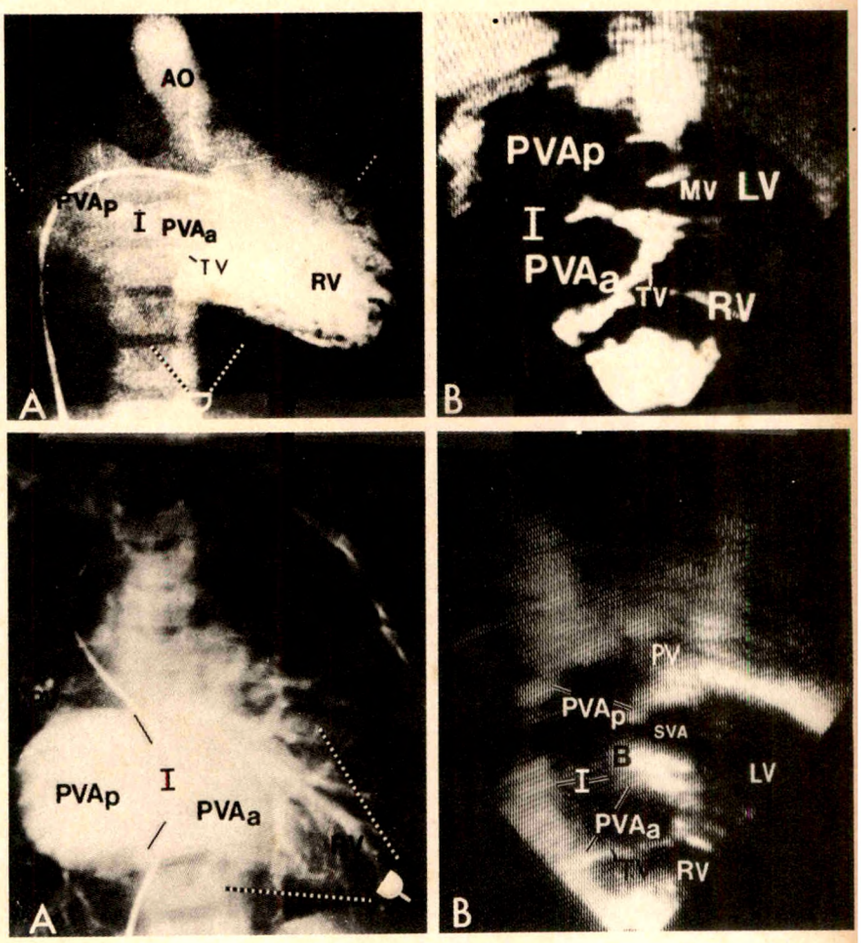

FIGURE 10. Top panel, Case 16. **A,** pulmonary venous angiogram and **B,** subxiphoid sector scan with severe tricuspid regurgitation requiring tricuspid valve (TV) replacement. Note almost horizontal malapposition of tricuspid valve leaflets in the echocardiogram and markedly enlarged segments of the pulmonary venous atrium (PVA). **Bottom panel,** Case 17. **A,** angiogram and **B,** sector scan, apical view, illustrating another patient with marked dilatation of the pulmonary venous atrial segments due to tricuspid regurgitation, who also required tricuspid valve replacement. Abbreviations as in Figures 1 and 4.

trimming the baffle and by patch enlargement of the lateral wall of the pulmonary venous atrium.[22,23] The hemodynamic severity of the pulmonary venous atrial stenosis was mild, as reflected by mildly elevated pulmonary arterial pressures, and the degree of stenosis was not considered significant enough to require reoperation.

Morphologic correlations between the lateral view angiograms and sector echocardiograms at the site of stenosis were good. However, angiographic quantitation of the narrowed segment was difficult and less accurate than the sector scan image quantitation because of superimposition of the anterior and posterior segments of the pulmonary venous atrium in the anterior and to some extent on the lateral angiogram, which obscured the isthmic region. The isthmic site on echocardiographic images was displaced posteriorly in the three Group III patients compared with the site in the control patients. This indicates that some cases of late stenosis of the pulmonary venous atrium may be due to contraction of the intraatrial baffle, which would result in the posterior displacement (closer to the pulmonary veins) of the isthmus.[20] Pulmonary veins could be clearly seen in all 17 patients and were unobstructed in the aforementioned patients. The diameter of the pulmonary venous isthmus was 0.9 to 1.0 cm, and this narrowed "waist" segment presumably was responsible for a mid diastolic murmur in these three patients. The continuous murmur recently described with pulmonary venous atrial stenosis[24] after the Mustard operation may be a late result of continued stenosis and marked reduction in the size of the posterior segment, which would result in loss of compliance and continued generation of systolic and diastolic pressure gradients similar to those with cor triatriatum.

Tricuspid regurgitation: This abnormality was confirmed at cardiac catheterization in each of our six Group IV patients and was shown to lead to a grossly enlarged pulmonary venous atrium with dilatation in all of its segments. The echocardiographic diagnosis of tricuspid regurgitation is indirect because regurgitation of the blood into the pulmonary venous atrium cannot be observed directly. Nonetheless, grossly increased dimensions of the pulmonary venous atrium with systolic pulsations and abnormalities of the tricuspid valve were associated in our study with angiographically proved tricuspid regurgitation. The mild narrowing of the pulmonary venous chamber isthmus noted in the control group was less obvious in these cases. In four cases the apposition of the tricuspid valve was almost horizontal and suggested that such apposition was due to dilatation of the right ventricle. Systolic pulsation of the posterior as well as the anterior segments of the pulmonary venous atrium suggested a marked degree

f tricuspid regurgitation. In one postoperative patient mmobilization of the septal leaflet of the tricuspid valve vas thought to lead to malapposition of the tricuspid eaflet resulting in tricuspid regurgitation. The recently leveloped technique of Doppler echocardiography ould be used for confirmation of tricuspid regurgitation y showing systolic turbulence in these dilated atria.

The cause of the tricuspid insufficiency in complete l-transposition is probably related to pre-, intra- and ostoperative factors.[25,26] Our pathologic studies show hat in nonsurgically treated complete transposition here is a marked tendency for abnormality in the entricular attachments of the tricuspid valve. Superposed on this is the factor of altered valve structure onsequent to hemodynamic stresses imposed on a ricuspid valve structure by systemic resistance. In some ases of transposition without ventricular septal defect, ricuspid insufficiency may develop because of the aforementioned factors exacerbated by increasing longevity. Where there is a ventricular septal defect there is a still greater tendency for the tricuspid valve to show abnormality. Here there may be malattachments of the tricuspid valve to the rim of the defect in some cases, as was demonstrated before surgical repair in four of our patients. There are also usually increased hemodynamic changes because of the defect. Intra- and postoperative damage to the tricuspid valve may result coincident with surgical repair (patching) of the ventricular septal defect when leaflet malattachments extend onto or across the rim of the defect. Thus, operative intervention in closure of the ventricular septal defect obviously can exacerbate the tendency toward tricuspid insufficiency. On occasion intrinsic right ventricular dysfunction may lead to tricuspid insufficiency, as was observed in one of our patients with an intact ventricular septum.

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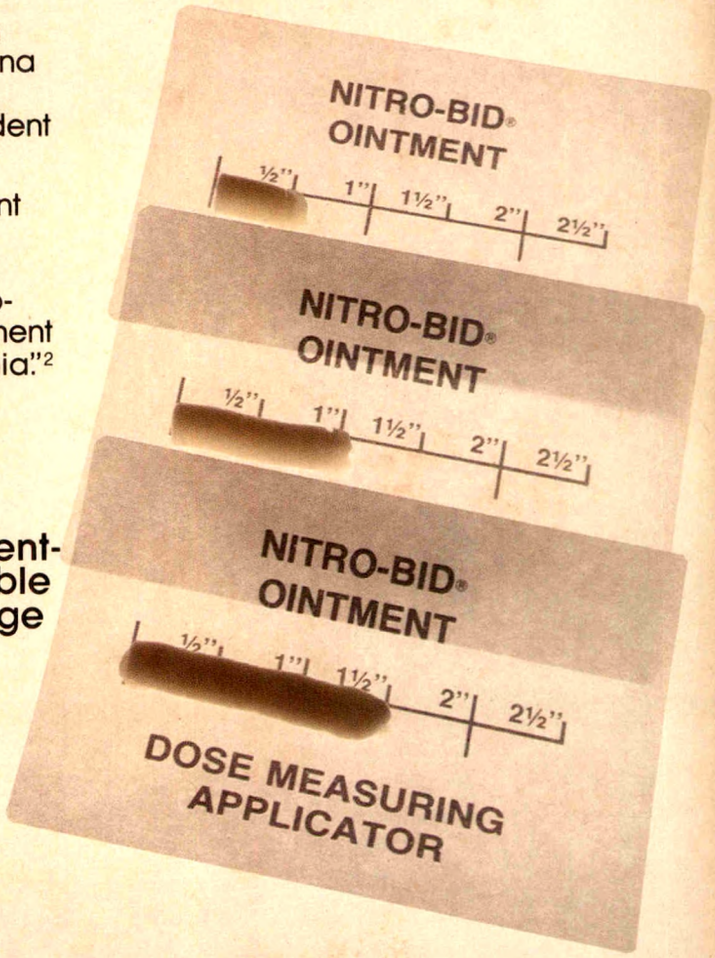

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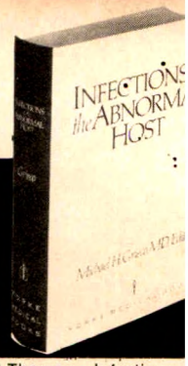

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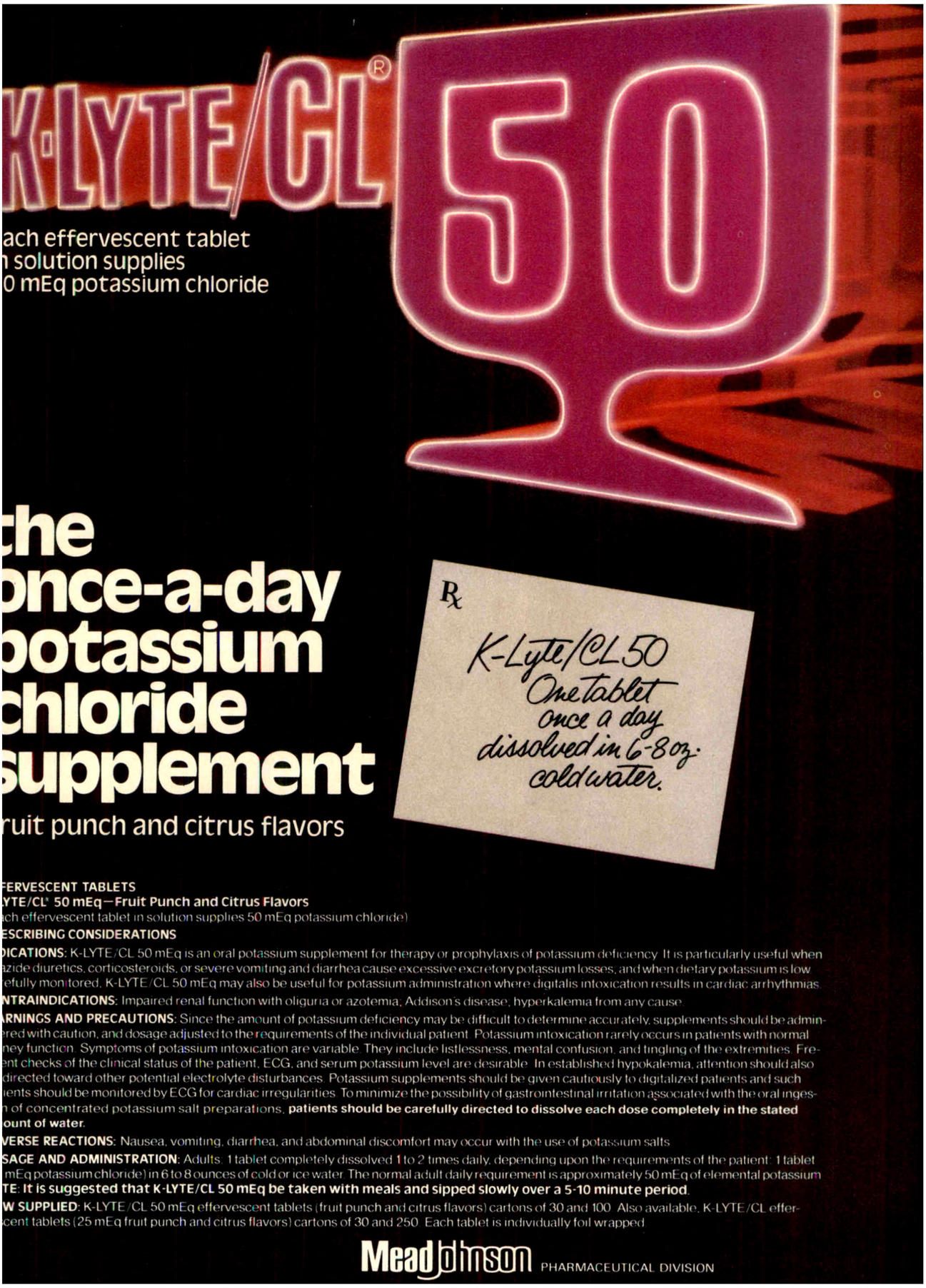

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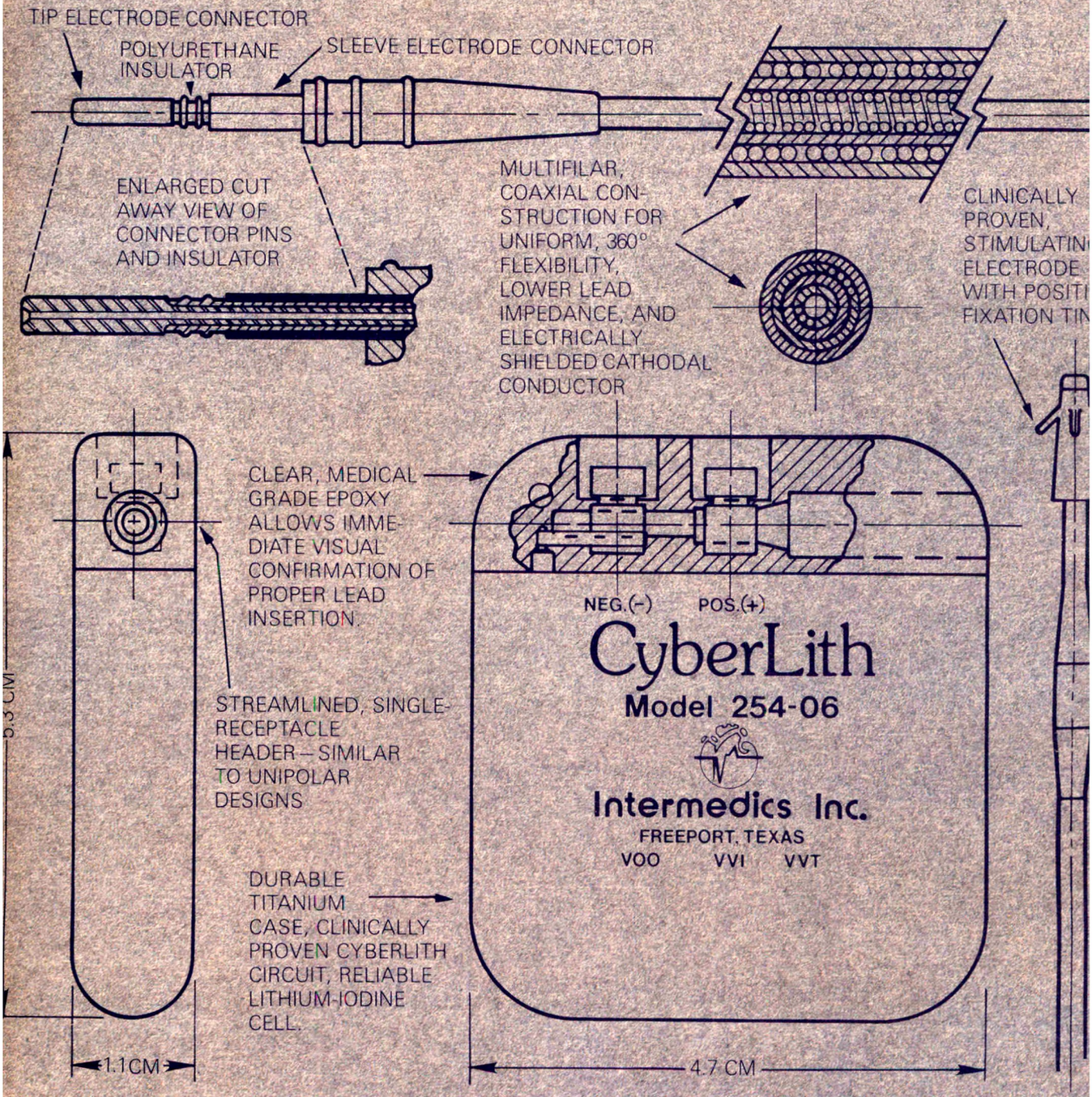

Intermedics Pulse Generators

INDICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacemaking are increasing as pacemakers become more sophisticated and as advanced methods for patient management become more widespread. Generally accepted indications for long-term cardiac pacing include but are not limited to: (1) sick sinus syndrome; (2) chronic, symptomatic drug-resistant sinus arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome(carotid sinus syncope). In addition, certain patients presenting with intractable, recurrent, congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias who have been shown to benefit from temporary cardiac pacing are considered candidates for permanent cardiac pacemaking.

The indications for permanent pacing in the presence of acute myocardial infarction have not yet

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Intermedics in-line technology is an entirely new concept in bipolar pacing. It permits a bipolar pacing system to be as thin, small, and lightweight as most unipolar systems; it offers remarkable convenience and simplicity of use; and it provides unparalleled immunity to non-cardiac signals.

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To find out more about the new convenience of bipolar pacing, contact your Intermedics representative or call us toll-free at 800/231-2330.

been rigorously defined. Factors to be considered include the location of the myocardial infarct, the presence or absence of symptoms, ventricular rate, mechanism of the arrhythmias, and response to therapy. In general, symotomatic drug-resistant bradyarrhythmias which impair cardiac output are considered indications for pacing in patients with acute myocardial infarction, regardless of infarct location.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

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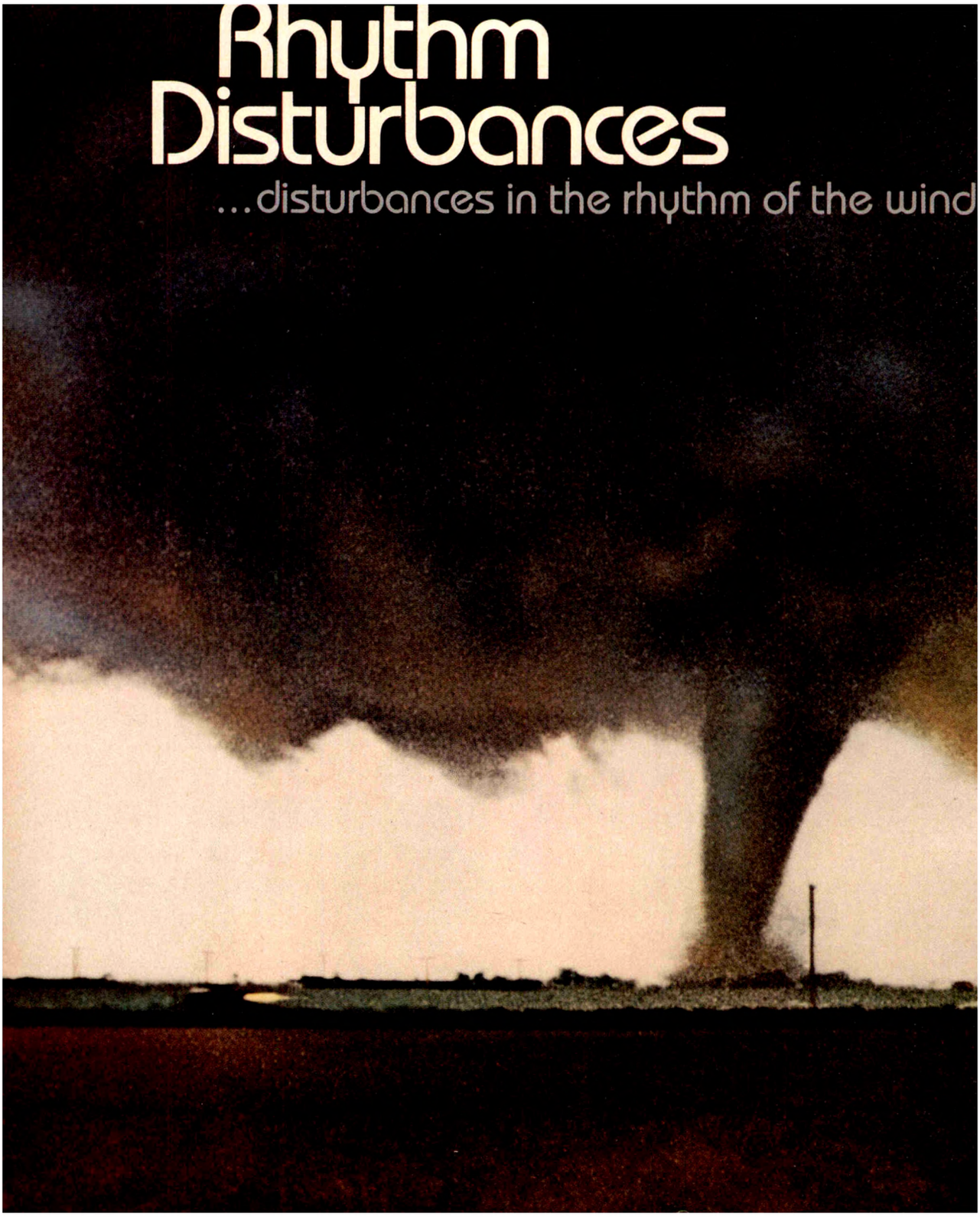
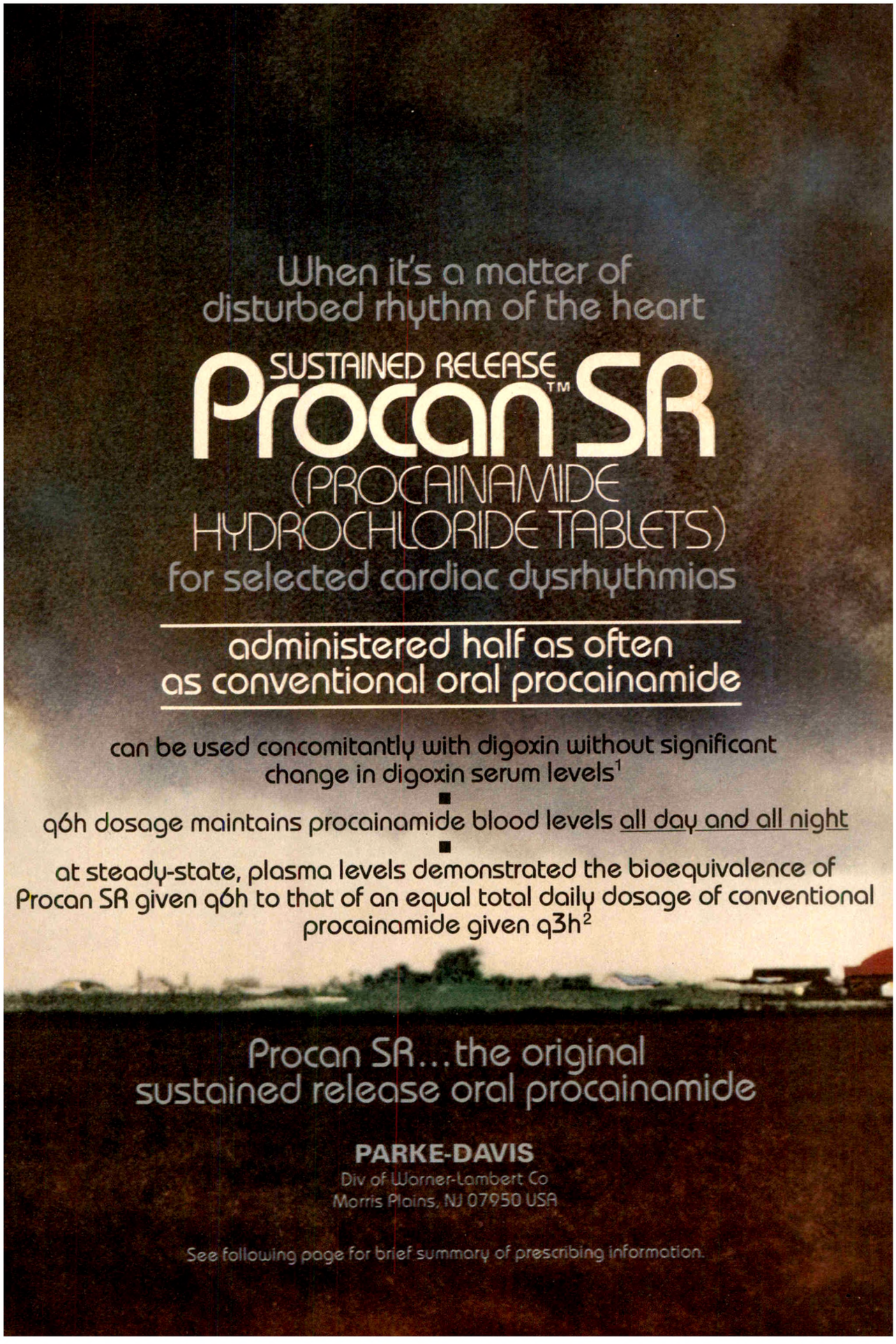

Rhythm
Disturbances
...disturbances in the rhythm of the wind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as conventional oral procainamide
can be used concomitantly with digoxin without significant
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See following page for brief summary of prescribing information.

Procan® SR
(procainamide hydrochloride tablets)
SUSTAINED RELEASE
Before prescribing, please see full prescribing information.
A Brief Summary follows:

The prolonged administration of procainamide often leads to the development of a positive antinuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate consideration of alternative antiarrhythmic therapy.

INDICATIONS: Oral procainamide is indicated in the treatment of premature ventricular contractions and ventricular tachycardia, atrial fibrillation, and paroxysmal atrial tachycardia.

CONTRAINDICATIONS: It has been suggested that procainamide be contraindicated in patients with myasthenia gravis. Hypersensitivity to the drug is an absolute contraindication; in this connection, cross-sensitivity to procaine and related drugs must be borne in mind. Procainamide should not be administered to patients with complete atrioventricular heart block. Procainamide is also contraindicated in cases of second-degree and third-degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: During administration of the drug, evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of an abnormal myocardium, procainamide may at times produce untoward responses. In atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed. Adequate digitalization reduces, but does not abolish, this danger. If myocardial damage exists, ventricular tachysystole is particularly hazardous. Correction of atrial fibrillation, with resultant forceful contractions of the atrium, may cause a dislodgement of mural thrombi and produce an embolic episode. However, it has been suggested that, in a patient who is already discharging emboli, procainamide is more likely to stop than to aggravate the process.

Attempts to adjust the heart rate in a patient who has developed ventricular tachycardia during an occlusive coronary episode should be carried out with extreme caution. Caution is also required in marked disturbances of atrioventricular conduction such as A-V block, bundle branch block, or severe digitalis intoxication, where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation.

Because patients with severe organic heart disease and ventricular tachycardia may also have complete heart block, which is difficult to diagnose under these circumstances, this complication should always be kept in mind when treating ventricular arrhythmias with procainamide. If the ventricular rate is significantly slowed by procainamide without attainment of regular atrioventricular conduction, the drug should be stopped and the patient re-evaluated because asystole may result under these circumstances.

In patients receiving normal dosage, but who have both liver and kidney diseases, symptoms of overdosage (principally ventricular tachycardia and severe hypotension) may occur due to drug accumulation.

Instances of a syndrome resembling lupus erythematosus have been reported in connection with maintenance procainamide therapy. The mechanism of this syndrome is uncertain. Polyarthralgia, arthritis, and pleuritic pain are common symptoms; to a lesser extent, fever, myalgia, skin lesions, pleural effusion, and pericarditis may occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia have been reported which may be related to this syndrome. Patients receiving procainamide for extended periods of time, or in whom symptoms suggestive of a lupus-like reaction appear, should have antinuclear antibody titers measured at regular intervals. The drug should be discontinued if there is a rising titer (antinuclear antibody) or clinical symptoms of LE appear. The LE syndrome may be reversible upon discontinuation of the drug. If discontinuation of the drug does not cause remission of the symptoms, steroid therapy may be effective. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not controllable by other antiarrhythmic agents, steroid suppressive therapy may be used concomitantly with procainamide. It is recommended that tests for lupus erythematosus be carried out at regular intervals in patients receiving maintenance procainamide therapy.

ADVERSE REACTIONS: Hypotension following oral administration is rare.

Large oral doses of procainamide may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported (see PRECAUTIONS). Reactions consisting of fever and chills have also been reported, including a case with fever and chills plus nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Bitter taste, diarrhea, weakness, mental depression, giddiness, and psychosis with hallucinations have been reported. The possibility of such untoward effects should be borne in mind.

Hypersensitivity reactions, such as angioneurotic edema and maculopapular rash have also occurred.

Agranulocytosis has occasionally followed the repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy. The patient should be instructed to report any soreness of the mouth, throat, or gums, unexplained fever, or any symptoms of upper respiratory tract infection. If any of these should occur, and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately.

DOSAGE AND ADMINISTRATION: Procan SR (procainamide hydrochloride tablets) are a sustained-release product form. The duration of action of procainamide hydrochloride supplied in this sustained-release product form allows dosing at intervals of every six hours instead of the more frequent every-three-hour dosing interval required for standard preparations of oral procainamide hydrochloride. The convenient six-hour dosing schedule may encourage patient compliance.

Ventricular tachycardia—Treatment with standard procainamide hydrochloride is recommended until the tachycardia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1 g of standard procainamide hydrochloride followed thereafter by a total daily dosage of 50 mg/kg of body weight given at three-hour intervals. The suggested oral dosage for premature ventricular contractions is 50 mg/kg of body weight daily given in divided doses at three-hour intervals.

The suggested maintenance dosage of Procan SR is 50 mg/kg of body weight daily given in divided doses at six-hour intervals.

Although the dosage for each patient must be determined on an individual basis, the following may be used as a guide for providing the total daily dosage: patients weighing less than 55 kg (120 lb), 0.5 g every six hours; patients weighing between 55 and 91 kg (120 and 200 lb), 0.75 g every six hours; and patients weighing over 91 kg (200 lb), 1 g every six hours.

Atrial fibrillation and paroxysmal atrial tachycardia—Treatment with standard procainamide hydrochloride is recommended until the arrhythmia is interrupted or the limit of tolerance is reached. Maintenance may then be continued with Procan SR.

The suggested dosage is as follows: An initial dose of 1.25 g of standard procainamide hydrochloride may be followed in one hour by 0.75 g if there have been no electrocardiographic changes. Standard procainamide hydrochloride may then be given at a dosage of 0.5 g to 1 g every two hours until interruption of the arrhythmia or the tolerance limit is reached.

The suggested maintenance dosage for Procan SR is 1 g every six hours.

If procainamide therapy is continued for appreciable periods, electrocardiograms should be made occasionally to determine the need for the drug.

HOW SUPPLIED: N 0071-0202 Procan SR 250 mg. Each sustained-release tablet contains 250 mg procainamide hydrochloride. Available in bottles of 100 tablets and in unit-dose packages of 100 (10 strips of 10 tablets each).

N 0071-0204 Procan SR 500 mg. Each sustained-release, scored tablet contains 500 mg procainamide hydrochloride. Available in bottles of 100 tablets and in unit-dose packages of 100 (10 strips of 10 tablets each).

ZD

References: 1. Leahey EB Jr, Reiffel JA, Giardina E-GV, et al: The effect of quinidine and other oral antiarrhythmic drugs on serum digoxin. *Ann Intern Med* 92:605-608, May 1980.
2. Smith TC, Kinkel AW: Plasma levels of procainamide after administration of conventional and sustained-release preparations. *Curr Therap Res* 27: 217- 228, 1980.

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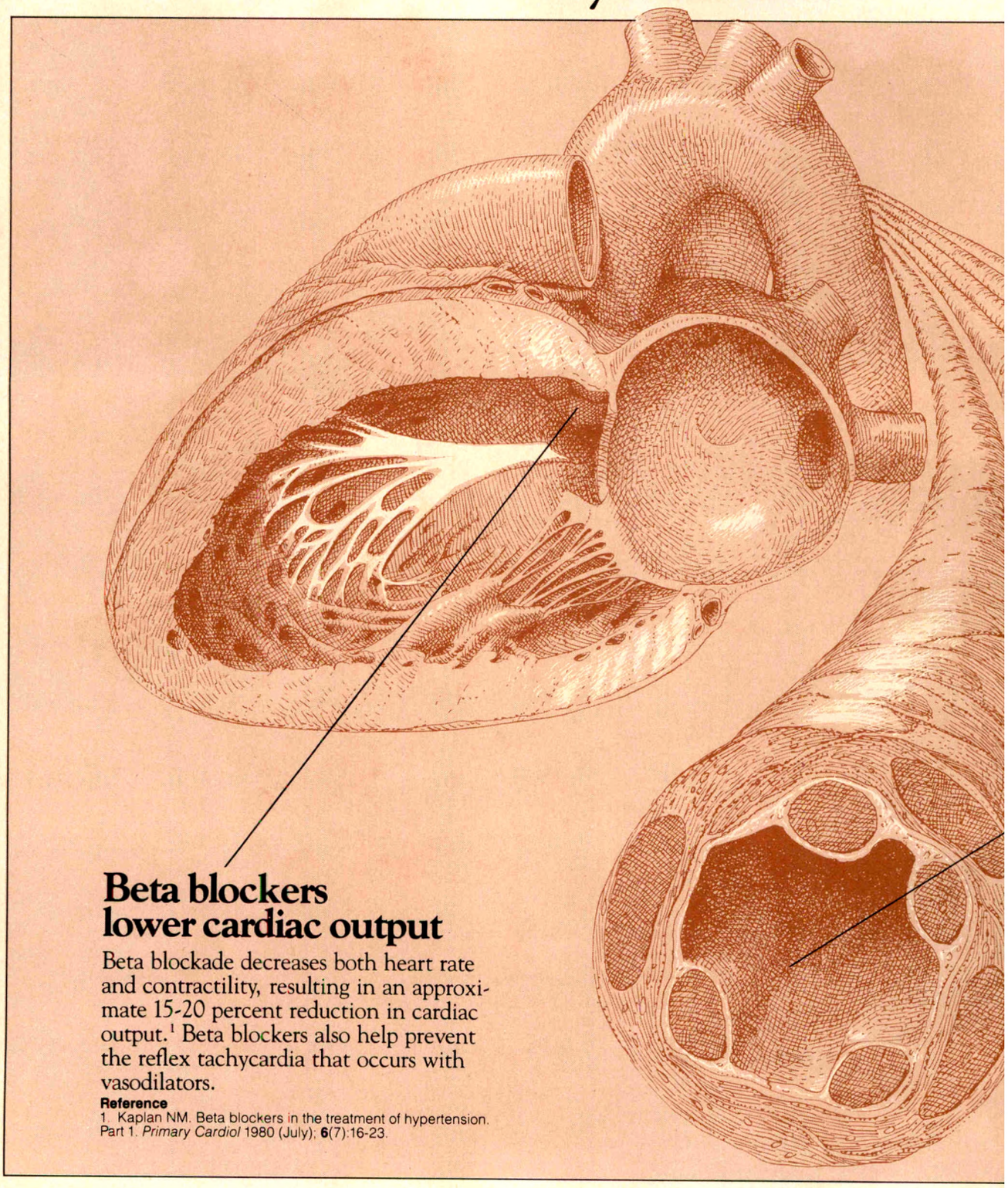
Apresoline
hydralazine



Beta blockers lower cardiac output

Beta blockade decreases both heart rate and contractility, resulting in an approximate 15-20 percent reduction in cardiac output.[1] Beta blockers also help prevent the reflex tachycardia that occurs with vasodilators.

Reference

1. Kaplan NM. Beta blockers in the treatment of hypertension. Part 1. *Primary Cardiol* 1980 (July); **6**(7):16-23.

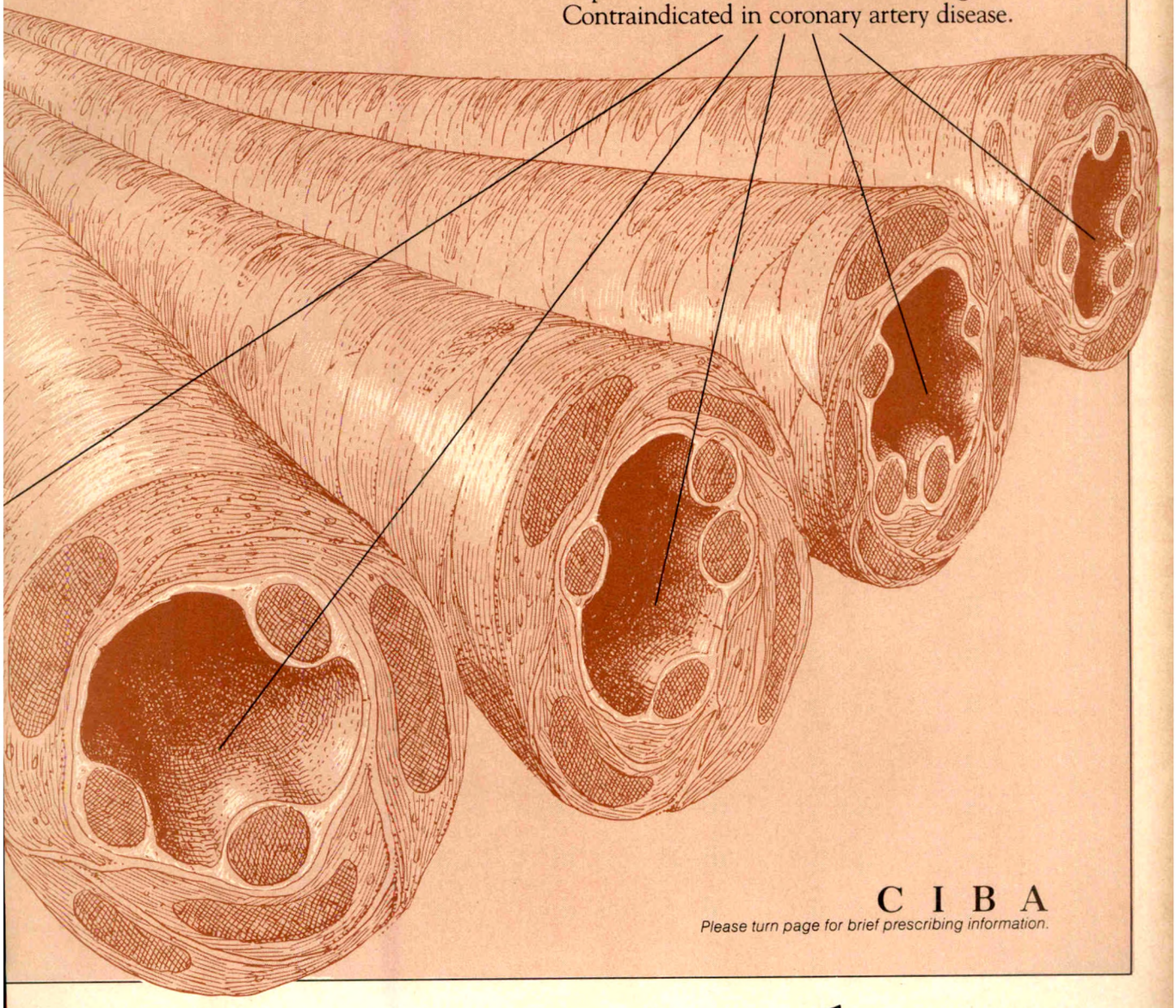
Where today's action is in

[illegible] beta blocker

Apresoline lowers peripheral resistance

By relaxing smooth muscles in the walls of peripheral arterioles—an effect lacking in a beta blocker—Apresoline acts to lower elevated peripheral resistance.

As with any antihypertensive agent, Apresoline should be used with caution in patients with advanced renal damage. Contraindicated in coronary artery disease.



CIBA

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antihypertensive therapy

Apresoline® hydrochloride
hydralazine hydrochloride USP
TABLETS

INDICATIONS
Essential hypertension, alone or as an adjunct.

CONTRAINDICATIONS
Hypersensitivity to hydralazine; coronary artery disease; and mitral valvular rheumatic heart disease.

WARNINGS
Hydralazine may produce in a few patients a clinical picture simulating systemic lupus erythematosus. In such patients hydralazine should be discontinued unless the benefit-to-risk determination requires continued antihypertensive therapy with this drug. Symptoms and signs usually regress when the drug is discontinued but residua have been detected many years later. Long-term treatment with steroids may be necessary. Complete blood counts, L.E. cell preparations, and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine even though the patient is asymptomatic. These studies are also indicated if the patient develops arthralgia, fever, chest pain, continued malaise or other unexplained signs or symptoms. A positive antinuclear antibody titer and/or positive L.E. cell reaction requires that the physician carefully weigh the implications of the test results against the benefits to be derived from antihypertensive therapy with hydralazine.
Use MAO inhibitors with caution in patients receiving hydralazine.
When other potent parenteral antihypertensive drugs, such as diazoxide, are used in combination with hydralazine, patients should be continuously observed for several hours for any excessive fall in blood pressure. Profound hypotensive episodes may occur when diazoxide injection and Apresoline (hydralazine hydrochloride) are used concomitantly.

Usage in Pregnancy
Animal studies indicate that hydralazine is teratogenic in mice, possibly in rabbits, and not in rats. Teratogenic effects observed were cleft palate and malformations of facial and cranial bones. Although clinical experience does not include any positive evidence of adverse effects on the human fetus, hydralazine should not be used during pregnancy unless the expected benefit clearly justifies the potential risk to the fetus.

PRECAUTIONS
Myocardial stimulation produced by Apresoline can cause anginal attacks and ECG changes of myocardial ischemia. The drug has been implicated in the production of myocardial infarction. It must, therefore, be used with caution in patients with suspected coronary artery disease.
The "hyperdynamic" circulation caused by Apresoline may accentuate specific cardiovascular inadequacies. An example is that Apresoline may increase pulmonary artery pressure in patients with mitral valvular disease. The drug may reduce the pressor responses to epinephrine.
Postural hypotension may result from Apresoline, but is less common than with ganglionic blocking agents. Use with caution in patients with cerebral vascular accidents.
In hypertensive patients with normal kidneys who are treated with Apresoline, there is evidence of increased renal blood flow and a maintenance of glomerular filtration rate. In some instances improved renal function has been noted where control values were below normal prior to Apresoline administration. However, as with any antihypertensive agent, Apresoline should be used with caution in patients with advanced renal damage.
Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect and the addition of pyridoxine to the regimen if symptoms develop.
Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.
The Apresoline tablets (10 and 100 mg) contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS
Adverse reactions with Apresoline are usually reversible when dosage is reduced. However, in some cases it may be necessary to discontinue the drug.
Common: Headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris.
Less frequent: Nasal congestion; flushing ; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremors; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paradoxical pressor response.

DOSAGE AND ADMINISTRATION
Initiate therapy in gradually increasing dosages; adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective levels.
The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.
In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect. In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.

C80-15 (1/80)

Consult complete product literature before prescribing.

126-6029-A

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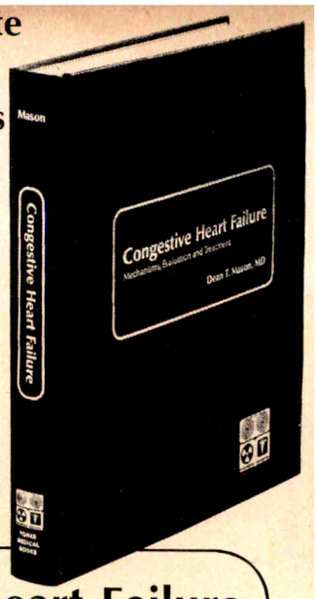

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Dean T. Mason, M.D.

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This presentation of recent advances in basic research and clinical progress has been highly acclaimed for its major contribution to the improvement of patient care. We invite you to see if you don't agree. Order and take 30 days to look over the book. If you're not totally satisfied, return it.

About the author . . . Dean T. Mason, M.D.

Professor of Medicine, Professor Physiology, Chief of Cardiovascular Medicine, University of California, School of Medicine, Davis.

President, American College of Cardiology; President, Western Society for Clinical Research.

Member of the American Board of Internal Medicine Cardiovascular Diseases.

Has authored more than 400 original articles on cardiovascular science and clinical cardiology.

Serves on the editorial boards of The American Journal of Cardiology, The Journal of Clinical Investigation, Circulation, Chest, Clinical Pharmacology and Therapeutics, Catheterization and Cardiovascular Diagnosis, and Heart and Lung.

Recipient of Experimental Therapeutics Award in 1973 from the American Society of Pharmacology and Experimental Therapeutics, the Research Awards in 1965 from the American Therapeutic Society, and the Theodore and Susan B. Cummings Humanitarian Awards in 1972, 1973, and 1975 from the U.S. State Department and the American College of Cardiology.

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Comparison of Hemodynamic Actions of Pirbuterol and Dobutamine on Cardiac Function in Severe Congestive Heart Failure

NAJAM A. AWAN, MD, FACC
KATHLEEN E. NEEDHAM, BS
MARK K. EVENSON, BS
DEAN T. MASON, MD, FACC

Davis and Sacramento, California

There is considerable interest in the development of beneficial oral inotropic agents for sustained ambulatory management of patients with severe chronic congestive heart failure. Therefore, the hemodynamic actions of the oral beta adrenergic receptor agonist pirbuterol and of intravenous dobutamine were compared in nine patients with severe heart failure. Both agents produced similar effects on ventricular pump function: The cardiac index was markedly increased from 1.8 to 2.6 liters/min per m^2 ($p < 0.005$) by dobutamine and from 1.8 to 2.9 liters/min per m^2 ($p < 0.001$) by pirbuterol; stroke index was increased from 24 to 32 ml/beat per m^2 ($p < 0.02$) by dobutamine and from 23 to 35 ml/beat per m^2 ($p < 0.001$) by pirbuterol; the stroke work index was increased from 19 to 27 g-m/m^2 ($p < 0.005$) by dobutamine and from 20 to 28 g-m/m^2 ($p < 0.005$) by pirbuterol. However, although dobutamine did not change mean blood pressure or left ventricular filling pressure ($p > 0.05$), pirbuterol modestly decreased mean blood pressure from 83 to 75 mm Hg ($p < 0.02$) and moderately decreased left ventricular filling pressure from 23 to 18 mm Hg ($p < 0.005$). Dobutamine reduced total systemic vascular resistance 22 percent from 2,049 to 1,582 dynes s cm^{-5} ($p < 0.001$), whereas pirbuterol reduced this index 42 percent ($p < 0.05$ versus dobutamine) from 2,068 to 1,150 dynes s cm^{-5}. Neither agent altered heart rate or the heart rate-systolic blood pressure product ($p > 0.05$).

Thus, oral pirbuterol has dobutamine-like beneficial hemodynamic effects on left ventricular pump function but causes a greater decrease in total systemic vascular resistance consistent with the combined inotropic and peripheral vasodilator actions of this oral beta adrenergic receptor agonist. These salutary hemodynamic responses suggest that oral pirbuterol may be useful for the prolonged treatment of severe chronic congestive heart failure.

The recent availability of potent oral vasodilators[1–4] has greatly improved ambulatory therapy of severe chronic congestive heart failure. Thereby the incorporation of systemic vasodilators into the conventional therapeutic regimens of digitalis and diuretic drugs[1–4] results in highly beneficial augmentation of cardiac pump function while ventricular preload is simultaneously decreased.[2,4–6] However, although cardiac contractility is well recognized as a fundamental regulator of cardiac pump performance,[7] the use of digitalis in the setting of severe congestive heart failure is accompanied by only modest augmentation of this major determinant of ventricular function.[7] Thus, there is considerable continuing interest in the development of safe and effective oral inotropic agents, used alone or in combination with potent systemic vasodilators, for sustained enhancement of the performance of the failing heart. Accordingly, we evaluated the hemodynamic effects of the new oral beta adrenergic receptor agonist pirbuterol on cardiac function, and compared the actions of this agent with those of intravenous dobutamine in patients with severe chronic congestive heart failure.

From the Section of Cardiovascular Medicine, Departments of Medicine and Physiology, University of California at Davis School of Medicine and Sacramento Medical Center, Davis and Sacramento, California. This study was supported in part by Program Project Grant HL-14780 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and California Chapters of the American Heart Association, Dallas, Texas. Manuscript received August 4, 1980; revised manuscript received September 30, 1980, accepted October 6, 1980.

Address for reprints: Najam A. Awan, MD, Section of Cardiovascular Medicine, University of California School of Medicine, Davis, California 95616.

Methods

Study patients (Table I): Nine patients (seven men and two women, mean age 59.5 years) with severe chronic congestive heart failure constituted the study group. The cause of chronic left ventricular dysfunction was ischemic heart disease with previous myocardial infarction (3 or more months earlier) documented clinically, electrocardiographically and angiographically in all patients. Significant valvular heart disease was carefully excluded in all. All patients had severe congestive heart failure despite administration of maximal doses of digoxin and diuretics, the mean left ventricular ejection fraction being 0.20. To maintain a stable clinical and hemodynamic state during the study, the usual doses of the daily medications were administered in the evenings throughout the investigation.

Cardiac catheterization: All nine patients underwent right heart catheterization with placement of the balloon-tipped thermodilution Swan-Ganz catheter in the pulmonary artery for assessment of cardiac performance. In each of these patients intraarterial blood pressure, pulmonary arterial pressures and triplicate thermodilution cardiac outputs were measured. Pulmonary arterial diastolic pressure was confirmed to be identical to pulmonary wedge pressure and was thereafter used to measure left ventricular filling pressure (LVFP). The following variables of cardiac performance were calculated: total systemic vascular resistance (TSVR, dynes s cm^{-5}) from [(MBP − RA) × 80]/CO, where MBP is mean blood pressure, RA is mean right atrial pressure and 80 is the conversion factor for converting units of resistance into dynes; stroke work index (SWI, g-m/m^2) from (MBP − LVFP) × SI × 0.0136, where SI is stroke index (ml/beat per m^2); and double product (mm Hg/min) from SBP × HR, where SBP is systolic blood pressure (mm Hg) and HR is heart rate (beats/min). Hemodynamic stability was confirmed in each patient by obtaining control measurements at 30 minutes and immediately before drug administration.

Drug administration: The study design consisted of sequential but randomized administration of a single dose of oral pirbuterol (0.4 mg/kg) or intravenous dobutamine infusion (maximal dose 20 μg/kg per min) titrated individually (mean dose [± standard error of the mean] 11 ± 3 μg/kg per min) to obtain optimal cardiac function (cardiac output 20 percent or greater with ± 5 beats/min change in heart rate). Thereby five patients received dobutamine as the initial drug (Group I) and four patients received pirbuterol first (Group II). Patients in Group I received pirbuterol at least 4 hours after dobutamine infusion when the basal hemodynamic state was reestablished after administration of dobutamine. Patients in Group II received dobutamine 36 to 48 hours after evaluation of responses to oral pirbuterol. The peak effects of the oral agent (1 to 2 hours after administration of pirbuterol) were then compared with the optimal effects of intravenous dobutamine.

Statistical analysis: Statistical data were analyzed using Student's *t* test for paired data and analysis of variance.

Results

Heart rate and blood pressure (Fig. 1): Control hemodynamic variables before administration of dobutamine were similar ($p > 0.05$) to the prepirbuterol values. The control heart rate of 79 ± 5 beats/min was not changed ($p > 0.05$) by intravenous dobutamine or oral pirbuterol. Mean systemic blood pressure was unaltered by dobutamine (control 77 ± 5, dobutamine 80 ± 6 mm Hg, $p > 0.05$), while oral pirbuterol caused a modest decrease in this variable from 83 ± 5 to 75 ± 4 mm Hg ($p < 0.02$).

Left ventricular filling pressure (Fig. 2): Although the average left ventricular filling pressure decreased during dobutamine infusion from 23 ± 3 to 19 ± 3 mm Hg, this change was not statistically significant ($p > 0.05$) because of the marked individual differences in the response of this variable in our patients. However, the abnormally elevated left ventricular filling pressure was modestly reduced by pirbuterol from 23 ± 3 to 18 ± 3 mm Hg ($p < 0.005$), and this variable decreased in most of the patients. Nevertheless, the percent decrease in left ventricular filling pressure of 24 ± 7 percent after pirbuterol did not differ significantly ($p > 0.05$) from the 18 ± 6 percent decrease produced by dobutamine.

Cardiac output (Fig. 3 and 4): Both pirbuterol and dobutamine markedly increased cardiac pump performance. Dobutamine increased the low control cardiac index of 1.8 ± 0.2 to 2.6 ± 0.3 liters/min per m^2 ($p < 0.005$), whereas oral pirbuterol increased this index from 1.8 ± 0.2 to 2.9 ± 0.3 liters/min per m^2 ($p < 0.001$). All patients given intravenous dobutamine and oral pirbuterol had an increase in cardiac index. Further, the percent increase in cardiac index was similar after pir-

TABLE I

Pretreatment Characteristics of Nine Patients

Case	Age (yr)	Diagnosis	NYHA Class	EF	Daily Therapy (mg)
1	32	Ant MI	III	0.20	Dig, Fur 240
2	69	Ant MI	IV	0.39	Dig, Fur 160
3	69	Ant MI	III	0.14	Dig, Fur 320
4	65	Ant MI	IV	0.17	Dig, Fur 480
5	54	Ant MI	III	0.23	Dig, Fur 240
6	59	Ant and Inf MI	IV	0.14	Dig, Fur 240
7	64	Ant and Inf MI	III	0.21	Dig, Fur 200, Tri 100
8	64	Ant and Inf MI	III	0.17	Dig, Fur 320
9	60	Ant MI	III	0.12	Dig, Fur 320

Ant = anterior; Dig = digoxin, 0.25 mg; EF = left ventricular ejection fraction; Fur = furosemide; Inf = inferior; MI = old myocardial infarction; NYHA = New York Heart Association functional class[8]; Tri = triamterene.

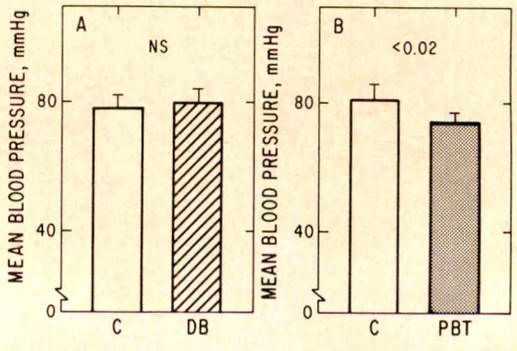

FIGURE 1. Effects of intravenous dobutamine (DB) (**panel A**) and oral pirbuterol (PBT) (**panel B**) on systemic blood pressure (mean ± standard error of the mean). C = control; NS = not significant.

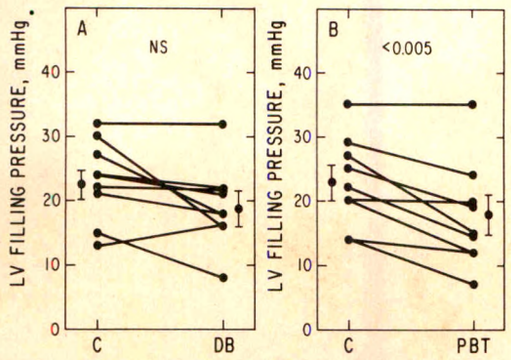

FIGURE 2. Effects of dobutamine (DB) (**panel A**) and pirbuterol (PBT) (**panel B**) on left ventricular (LV) filling pressure. C = control; NS = not significant.

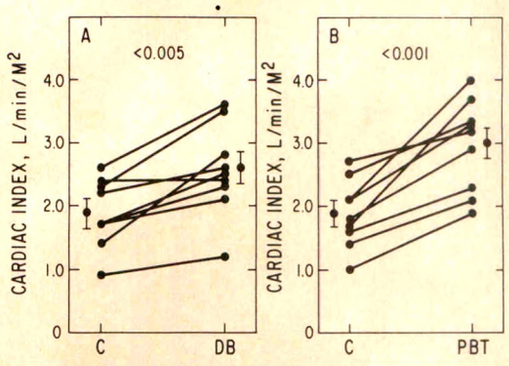

FIGURE 4. Peak effects of dobutamine (DB) (**panel A**) and pirbuterol (PBT) (**panel B**) on cardiac index. C = control.

buterol (38 ± 4 percent) and dobutamine (31 ± 4 percent) ($p > 0.05$). Concomitantly, because the heart rate remained unchanged, the stroke volume index was equally enhanced by both agents. The control stroke index of 24 ± 3 was increased to 32 ± 4 ml/beat per m^2 ($p < 0.02$) by dobutamine and from 23 ± 2 to 35 ± 4 ml/beat per m^2 ($p < 0.001$) by oral pirbuterol.

Stroke work index and systemic vascular resistance (Fig. 5): The stroke work index increased ($p < 0.005$) with both drugs (control 19 ± 5, dobutamine 27 ± 6; control 20 ± 3, pirbuterol 28 ± 6 g-m/m^2). Moreover, total systemic vascular resistance decreased ($p < 0.001$) with both agents (control 2,049 ± 341, dobutamine 1,582 ± 341; control 2,068 ± 291, pirbuterol 1,150 ± 170 dynes s cm^{-5}). However, despite similar effects on preload and cardiac pump function, the 42 ± 4 percent reduction in this variable produced by pirbuterol exceeded the 22 ± 3 percent decrease produced by intravenous administration of dobutamine ($p < 0.05$).

The control double product (heart rate × systolic blood pressure) of 10,040 mm Hg/min was unchanged ($p > 0.05$) by both agents. Moreover, neither drug caused left ventricular ischemia or increased ventricular arrhythmia.

Discussion

Similarity of pirbuterol and dobutamine salutary effects: This investigation clearly demonstrates that oral pirbuterol produces a marked increase in cardiac pump function in patients with severe congestive heart failure. The unique feature of this study is that it reveals that the major salutary actions of pirbuterol on left ventricular function are similar to the beneficial effects of the well recognized intravenous inotropic agent dobutamine. Thus, the substantial increase in cardiac index (Fig. 4B) and the moderate decrease in left ventricular filling pressure (Fig. 2B) caused by oral pirbuterol were similar to the beneficial augmentation in these variables (Fig. 2A and 4A) during dobutamine infusion. Similarly, stroke index and stroke work index were equally increased by the two drugs.

Differences between pirbuterol and dobutamine: Important differences in the extent of hemodynamic effects on some variables were also perceived. Thus, a moderate decrease in mean systemic blood pressure occurred with oral pirbuterol (Fig. 1B). Further, although the average decreases in elevated left ventricular filling pressure produced by the two drugs were equal (Fig. 3B), pirbuterol consistently produced a modest

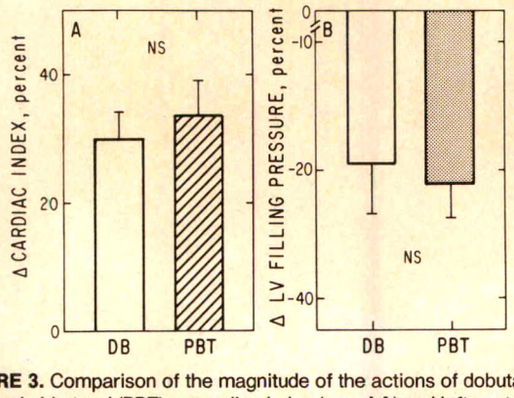

FIGURE 3. Comparison of the magnitude of the actions of dobutamine (DB) and pirbuterol (PBT) on cardiac index (**panel A**) and left ventricular (LV) filling pressure (**panel B**). Δ = change; NS = not significant.

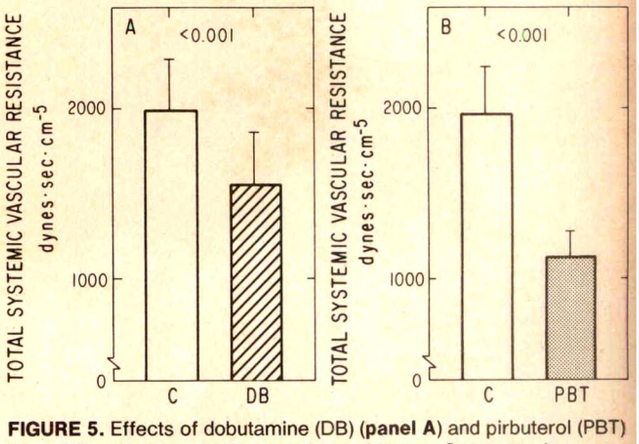

FIGURE 5. Effects of dobutamine (DB) (**panel A**) and pirbuterol (PBT) (**panel B**) on total systemic vascular resistance. C = control.

decrease in this variable (Fig. 2B), whereas the dobutamine responses were more variable (Fig. 2A). Additionally, although pirbuterol resulted in a beneficial improvement in left ventricular pump output similar to that produced by dobutamine, with pirbuterol the improvement was accompanied by a greater decrease in total systemic vascular resistance (Fig. 5).

Mechanisms of action: These observations of similar pump actions but disparate peripheral vascular actions of the two agents may be importantly related to the mechanisms of action of the drugs. Dobutamine produces predominantly $beta_1$ adrenergic receptor agonist effects,[7–10] thereby augmenting myocardial contractility[7] and cardiac pump output.[9–11] In contrast, oral pirbuterol is more nonselective,[12] particularly in the larger doses used in our patients with heart failure, leading to stimulation of $beta_1$ as well as $beta_2$ adrenergic receptors.[13,14] Therefore, the beneficial effects of pirbuterol are probably caused by combined central inotropic and peripheral vasodilator actions of this agent. This concept of simultaneous vasorelaxant and inotropic effects of the oral agent are consistent with our results. Accordingly, despite equal effects of the two drugs on left ventricular pump function, pirbuterol produced a greater reduction in total systemic vascular resistance than did dobutamine (Fig. 5). Similarly, although the latter drug did not change systemic blood pressure, this variable decreased modestly after pirbuterol ingestion (Fig. 1). Nevertheless, the precise extent of the contribution of these two actions, inotropic and vasodilator, to the pharmacodynamic profile of this oral beta agonist are difficult to quantify, and it remains possible that vasodilator actions of pirbuterol may predominate. Indeed, a similar hemodynamic response is well known with some pure arteriolar relaxing agents.[1] Despite uncertainty concerning the exact mechanism of action of the drug, our results demonstrate that oral pirbuterol provides dobutamine-like beneficial hemodynamic effects indicating a useful potential for outpatient therapy of severe congestive heart failure with this agent.

Mechanism of reduced left ventricular preload: Concerning the possible mechanisms of the reduced left ventricular preload noted in this study, a decrease in end-systolic volume associated with augmented contractility and enhanced left ventricular ejection fraction is known to decrease left ventricular filling pressure.[15] Thus, the reduction in this variable noted in some patients during infusion of dobutamine (Fig. 2A) is probably related to the aforementioned mechanism of improved ejection fraction and elevated cardiac output. However, a decrease in cardiac preload was more consistently noted after pirbuterol administration (Fig. 2B) despite similar enhancement of the cardiac output as dobutamine. Further, we have previously shown[14] that oral pirbuterol causes a decrease in venous tone, thereby reducing cardiac preload. Thus, it is probable that the pirbuterol-effected fall in left ventricular filling pressure is the result of augmented myocardial contractility, decreasing end-systolic volume, combined with the beneficial venodilator actions of the drug. Regardless of the mechanism of this helpful decrease in elevated left ventricular filling pressure, the useful preload-lowering effect of pirbuterol is usually of modest magnitude. Therefore, during ambulatory therapy of severe heart failure it may sometimes be necessary to combine pirbuterol with an effective venodilator agent to provide salutary improvement in congestive symptoms.

Therapeutic implications: Although these salutary hemodynamic actions of oral pirbuterol are encouraging, the determination of precise therapeutic usefulness of this agent in the prolonged management of patients with severe chronic congestive heart failure must await further trials. Initial experience with this agent at our institutions did not demonstrate precipitation of increased ventricular arrhythmia or exacerbation of myocardial ischemia. Accordingly, if further controlled evaluation confirms continued efficacy and safety of this agent, the incorporation of oral pirbuterol into the pharmacologic approach to the management of severe chronic congestive heart failure may represent a significant therapeutic advance.

Acknowledgment

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Hemodynamic Effects of Intravenous Prenalterol in Severe Heart Failure

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Nine patients with chronic severe low output heart failure (radionuclide left ventricular ejection fraction 17 ± 5 percent [mean ± standard deviation], left ventricular filling pressure 26 ± 6 mm Hg, cardiac index 1.9 ± 0.4 liters/min per m^2, left ventricular stroke work index 18 ± 6 g-m/m^2) from various causes were treated with intravenous prenalterol (a new catecholamine-like inotropic agent) in doses of 1, 4 and 8 mg. Significant hemodynamic improvement occurred as measured by increased left ventricular ejection fraction (to 26 ± 4 percent), decreased left ventricular filling pressure (to 21 ± 8 mm Hg) and increased cardiac index (to 2.4 ± 0.6 liters/min per m^2) and left ventricular stroke work index (to 25 ± 8 g-m/m^2). Significant increases in heart rate (from 87 ± 18 to 91 ± 18 beats/min) and mean systemic arterial pressure (from 87 ± 8 to 92 ± 7 mm Hg) also occurred. Peak hemodynamic response occurred at various doses. Significant adverse effects associated with prenalterol consisted of increased ventricular ectopic beats in two patients and asymptomatic ventricular tachycardia in two patients. Thus, intravenous prenalterol produces hemodynamic improvement in patients with a chronic severe low output state but may be associated with increased ventricular ectopic activity.

Prenalterol (levorotatory form of 1-isopropylamino-3-[p-hydroxyphenoxy]-2-propanol hydrochloride) is a new catecholamine-like cardiac inotropic agent which has been shown in animal[1,2] and human[3–9] studies to possess relatively selective $beta_1$ adrenergic stimulating properties, resulting in a positive inotropic response with acceptable chronotropic and vasoactive properties. Because it is effective both orally and parenterally, it has been proposed for use in the therapy of both acute and chronic heart failure, including potential use as an adjunct or substitute for cardiac glycoside therapy in selected patients. The current study was undertaken to provide an evaluation of the hemodynamic effects of intravenously administered prenalterol in patients with severe low output heart failure.

Methods

Study patients: Nine patients (mean age 59 ± 7 years) with chronic severe symptomatic heart failure (New York Heart Association[10] functional class II to IV; left ventricular filling pressure, determined from mean pulmonary arterial wedge pressure, greater than or equal to 16 mm Hg; and left ventricular ejection fraction less than or equal to 30 percent) were included. Seven of the nine patients were in the cardiac intensive care unit for management of heart failure at the time of investigation. Six patients had ischemic heart disease, two had idiopathic failure and one had alcoholic cardiomyopathy. The clinical diagnosis of severe left ventricular dysfunction was substantiated by cardiac catheterization with selective coronary angiography in seven patients, and in the remaining two patients it was supported by M mode echocardiography.

Before study, a complete history was obtained and physical examination was performed with emphasis placed on New York Heart Association functional class and signs of heart failure. Five patients were chronically digitalized with oral

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digoxin at the time of investigation in doses ranging from 0.125 to 0.25 mg daily. Serum digoxin levels in digitalized patients obtained within 1 to 6 days of prenalterol administration ranged from 0.26 to 1.05 mg/ml (mean 0.74). No patient had clinical evidence of digitalis toxicity. All patients required chronic diuretic therapy. Prior antiarrhythmic therapy in two patients (disopyramide, 100 mg orally four times daily, in Patient 8 and quinidine sulfate, 200 mg orally four times daily, in Patient 9), was continued throughout the study. Vasodilators were withheld for 24 hours. Digitalis and diuretic agents were administered at least 6 hours before and antiarrhythmic medications were withheld during administration of the investigational agent. Patients with unstable angina, acute myocardial infarction within 3 months or hypertrophic cardiomyopathy were excluded. The investigative protocol was approved by the Human Use Committee of the University of Michigan Medical Center, and written informed consent was obtained from each patient before study.

Hemodynamic measurements: All patients were studied in the postabsorptive state after placement of a flow-directed pulmonary arterial thermodilution catheter. Systemic arterial pressure was monitored by radial or brachial arterial catheter (seven patients) or sphygmomanometer (two patients). Heart rate was determined from the electrocardiogram. Other hemodynamic variables were determined as follows: Cardiac output was determined in eight patients by thermodilution technique (10 cc of iced 5 percent dextrose in water injected by pneumatic pump) and in one patient by indocyanine green using a Lexington cardiac output computer. The mean of triplicate thermodilution or duplicate green dye values was determined at each interval. Pulmonary arterial systolic and diastolic pressures and mean pulmonary arterial, mean pulmonary arterial wedge and mean right atrial pressures were obtained directly from the flotation catheter connected to Statham P23DB pressure transducers recorded on an Electronics for Medicine VR12 recorder. Derived hemodynamic variables were obtained from standard formulas. Left ventricular filling pressure was determined from mean pulmonary arterial wedge pressure.

Radionuclide studies: Left ventricular ejection fraction was determined by equilibrium radionuclide gated cardiac blood pool imaging using 10 to 20 mCi of technetium-99m for in vivo labeling of circulating red blood cells. A gamma camera oriented in the modified left anterior oblique position was used for cardiac blood pool imaging. Technically satisfactory radionuclide studies were obtained in eight of the nine patients.

Other laboratory studies: Continuous 24 hour electrocardiographic (Holter) monitoring was obtained on the day of the study for arrhythmia analysis. A minimum of 8 hours of electrocardiographic monitoring was recorded before administration of the investigational drug. Chest roentgenography, 12 lead electrocardiography, complete blood count, platelet count, reticulocyte count, prothrombin time, partial thromboplastin time, urine analysis and determination of SMA 12 blood chemistry values, electrolytes and cardiac enzymes (creatine kinase with isoenzyme pattern, lactic dehydrogenase with isoenzyme pattern and serum glutamic oxaloacetic transaminase analysis) were performed before administration of prenalterol. Analysis of all laboratory data except the chest roentgenogram was repeated after drug administration and compared with pretreatment values.

Prenalterol administration: After two control measurements in the resting state, intravenous prenalterol was administered through a peripheral intravenous line in doses of 1, 4 and 8 mg at 30 minute intervals. Each dose was given over 5 minutes by infusion pump, and hemodynamic measurements were performed over 5 minutes beginning 10 and 25 minutes after 1 and 4 mg doses and 10, 25 and 55 minutes after 8 mg doses. The mean of two baseline control values was used for comparison with values after drug administration.

Statistical analysis: All values were expressed as mean ± standard deviation. Statistical analysis was performed using the paired *t* test. A probability (p) value of less than or equal to 0.05 was considered statistically significant.

Results

Severe chronic impairment of left ventricular function was present in all patients. Eight of the nine patients had had symptoms of heart failure for at least 1 year and one patient had had such symptoms for 4 months. Six patients were in New York Heart Association functional class IV, two were in class III and one patient was in class II. Eight of the nine patients had a left ventricular third heart sound (S_3) at the time of study, and seven had received venous or arterial vasodilator therapy for refractory heart failure.

Hemodynamic effects of prenalterol: Hemodynamic data revealed significant improvement in cardiac index and left ventricular stroke work index and ejection fraction associated with a decrease in left ventricular filling pressure (Table I, Fig. 1). Statistically significant increases in systemic and mean arterial pressures and heart rate occurred as well. Diastolic arterial pressure and systemic arteriolar resistance did not change significantly. Pulmonary vascular resistance and mean right atrial pressure decreased significantly. Increases in right ventricular stroke work index were nearly statistically significant ($p < 0.06$). No significant differences were noted among the three doses, and the peak hemodynamic effect occurred variably after the 1, 4 or 8 mg doses.

Effect on ventricular arrhythmia: No adverse hemodynamic effects were noted except for a transient asymptomatic decrease in ejection fraction, cardiac index and stroke work index in Patient 4. Electrocardiographic monitoring revealed ectopic ventricular complexes during the control period in all patients. During subsequent drug administration, two patients had an increased number of ventricular ectopic complexes, and transient unsustained asymptomatic ventricular tachycardia developed in two patients. Patient 5 had had frequent three beat ventricular tachycardia before drug administration and a prolonged (172 beat) run of ventricular tachycardia after drug administration. Prenalterol administration was discontinued in this patient and no further ventricular tachycardia was noted on subsequent 24 hour monitoring. Patient 7 manifested a nine beat ventricular tachycardia after drug administration without previous or subsequent ventricular tachycardia. Both Patients 5 and 7 received concomitant digoxin therapy at the time of study. Prenalterol therapy was discontinued in Patient 6 after administration of 4 mg because the number of ventricular ectopic complexes increased.

Adverse effects: All patients tolerated prenalterol administration without subjective complaints of angina pectoris, palpitations, worsening shortness of breath or other symptoms. No electrocardiographic signs of in-

creased ischemia were noted during drug administration. Evaluation of laboratory values after drug administration revealed no adverse effects on hematologic, hepatic or cardiac variables, including cardiac enzyme analysis.

Discussion

Recent advances in the medical management of low output heart failure include the introduction of vasodilator therapy for ventricular preload and afterload reduction as well as the introduction of the potent new parenteral inotropic agents dopamine and dobutamine. However, the only oral inotropic agents currently available for clinical use are the cardiac glycosides, which are associated with a significant incidence of toxicity, including life-threatening cardiac arrhythmias.[11] Digitalis cardiac toxicity may be enhanced by the frequent concurrent administration of potassium-depleting diuretic drugs and quinidine, which significantly increases serum digoxin levels and thereby may increase myocardial glycoside concentration to toxic levels.[12] In addition, several investigators have suggested that chronic cardiac glycoside therapy may be ineffective in some patients with heart failure, as evidenced by a return to pretreatment hemodynamic status upon withdrawal of chronic digitalis therapy.[13–16]

TABLE I

Characteristics of Patients and Response to Prenalterol

	Patients										p Versus
	1	2	3	4	5*	6	7	8	9	Mean ± SD	Baseline
Age (yr) & sex	63M	53F	64F	56F	60F	48M	64M	55M	70M	59 ± 7	. . .
Cause of cardiomyopathy	Isch-emic	Alco-holic	Isch-emic	Idio-pathic	Isch-emic	Idio-pathic	Isch-emic	Isch-emic	Isch-emic	. . .	. . .
Heart rate (beats/min)											
Baseline	75	74	89	120	110	71	96	75	72	87 ± 18	<0.05
Maximal	80	83	106	122	. . .	90	102	75	68	91 ± 18	
Systolic arterial pressure (mm Hg)											
Baseline	116	110	135	118	102	128	135	108	104	117 ± 13	<0.004
Maximal	120	130	140	130	. . .	135	140	120	107	128 ± 11	
Mean arterial pressure (mm Hg)											
Baseline	90	94	84	87	74	92	97	88	74	87 ± 8	<0.007
Maximal	92	98	91	98	. . .	93	100	94	77	92 ± 7	
Diastolic arterial pressure (mm Hg)											
Baseline	78	86	62	71	62	78	78	75	60	72 ± 9	<0.09
Maximal	78	88	67	85	. . .	75	82	76	65	77 ± 8	
LVEF (%)											
Baseline	17	†	26	20	12	18	17	10	12	17 ± 5	<0.002
Maximal	26	†	31	21	. . .	29	25	21	26	26 ± 4	
LVSWI (g-m/m^2)											
Baseline	21	22	28	12	12	27	16	17	12	18 ± 6	<0.008
Maximal	28	21	30	17	. . .	40	22	28	15	25 ± 8	
Cardiac Index (liters/min per m^2)											
Baseline	1.9	1.8	2.7	1.8	2.0	2.0	1.8	1.4	1.4	1.9 ± 0.4	<0.015
Maximal	2.7	1.8	3.1	1.9	. . .	3.2	2.7	2.0	1.5	2.4 ± 0.6	
LVFP (mm Hg)											
Baseline	31	28	16	28	26	20	32	16	32	26 ± 6	<0.01
Minimal	25	25	18	23	. . .	11	30	7	29	21 ± 8	
PAP (mm Hg)											
Baseline	54	42	34	34	34	31	51	26	45	39 ± 9	<0.02
Minimal	41	40	36	30	. . .	22	49	17	40	34 ± 11	
SAR (dynes s cm^{-5})											
Baseline	. . .	2,229	1,460	1,786	1,449	1,446	2,133	2,802	1,780	1,872 ± 493	<0.11
Minimal	. . .	2,289	1,280	2,075	. . .	903	1,413	2,071	1,692	1,674 ± 502	
PAR (dynes s cm^{-5})											
Baseline	482	391	350	168	185	190	507	348	424	338 ± 129	<0.005
Minimal	208	246	320	125	. . .	82	201	209	327	215 ± 85	
RVSWI (gm/m^2)											
Baseline	15	8	10	3	5	9	8	5	7	8 ± 4	<0.06
Maximal	. . .	9	12	3	. . .	9	12	6	8	9 ± 3	
RAP (mm Hg)											
Baseline	10	16	10	18	12	6	18	8	20	13 ± 5	<0.01
Minimal	NA	12	10	15	. . .	5	12	4	18	11 ± 5	

* Patient 5 had ventricular tachycardia after a 1 mg infusion and was excluded from further analysis. † Technically unsatisfactory radionuclide cardiac blood pool scan.

LVEF = left ventricular ejection fraction; LVFP = left ventricular filling pressure; LVSWI = left ventricular stroke work index; NA = not available; PAP = mean pulmonary arterial pressure; PAR = pulmonary arteriolar resistance; RAP = mean right atrial pressure; RVSWI = right ventricular stroke work index; SAR = systemic arteriolar resistance.

Because cardiac glycosides remain less than ideal agents for chronic inotropic therapy of heart failure despite 2 centuries of use, other orally effective inotropic agents are being actively investigated.

Pharmacologic features of prenalterol: The new inotropic agent prenalterol is a derivative of phenol with a chemical structure resembling the catecholamine isoproterenol. The presumed mechanism of action is stimulation of cardiac beta$_1$ adrenergic receptors, which appears to be mediated directly since reserpine-treated animals maintain an inotropic response after administration of prenalterol.[1] It is effective both parenterally and orally and has relatively selective inotropic effects with a smaller effect on heart rate and systemic arterial pressure.

Animal studies by Carlsson et al.[1] demonstrated dose-dependent increases in the rate of rise of left ventricular pressure (dP/dt) after intravenous prenalterol with fewer chronotropic and arterial vasodilating properties than isoproterenol or terbutaline. Oral administration of 5 to 20 mg of prenalterol by Knaus et al.[3] to normal volunteers resulted in shortened systolic time intervals with significant increases in heart rate and systolic arterial pressure and a transient decrease in diastolic arterial pressure. Sinus arrhythmias increased significantly with no increase in ventricular or supraventricular extrasystoles. The inotropic effects of prenalterol in normal volunteers are blocked by the selective beta$_1$ adrenergic blocking agent metoprolol.[4] Pharmacokinetic data in normal volunteers demonstrated a mean plasma half-life of 2 hours after intravenous administration of prenalterol,[4] compared with a plasma half-life of 2 minutes for dobutamine.[17] Prenalterol's electrophysiologic properties include shortened atrioventricular nodal conduction time and atrial refractory period.[18]

Clinical hemodynamic effects of prenalterol: Previous clinical investigations in patients with cardiac disease have also demonstrated beneficial hemodynamic effects. Hutton et al.[6] demonstrated increased left ventricular dP/dt after intravenous administration of prenalterol in patients with ischemic heart disease without changes in heart rate or end-diastolic volume. Prenalterol reversed the decreased heart rate, blood pressure and cardiac output and the increased preejection period after adrenergic blockade with metoprolol following acute myocardial infarction.[5] A preliminary study of oral prenalterol in patients with severe heart failure (functional classes III and IV) showed beneficial effects on left ventricular filling pressure, cardiac index, ejection fraction and exercise tolerance.[7] Hypotension induced by spinal anesthesia has been reversed by prenalterol.[19] No significant adverse effects have previously been reported after administration of prenalterol.

The possibility that prolonged administration of prenalterol may be associated with a diminished response, a phenomenon noted with other adrenergic stimulants[20] including dobutamine,[21] has not been investigated. The hemodynamic effects of prenalterol compared with other inotropic agents such as dobutamine and dopamine have not been reported.

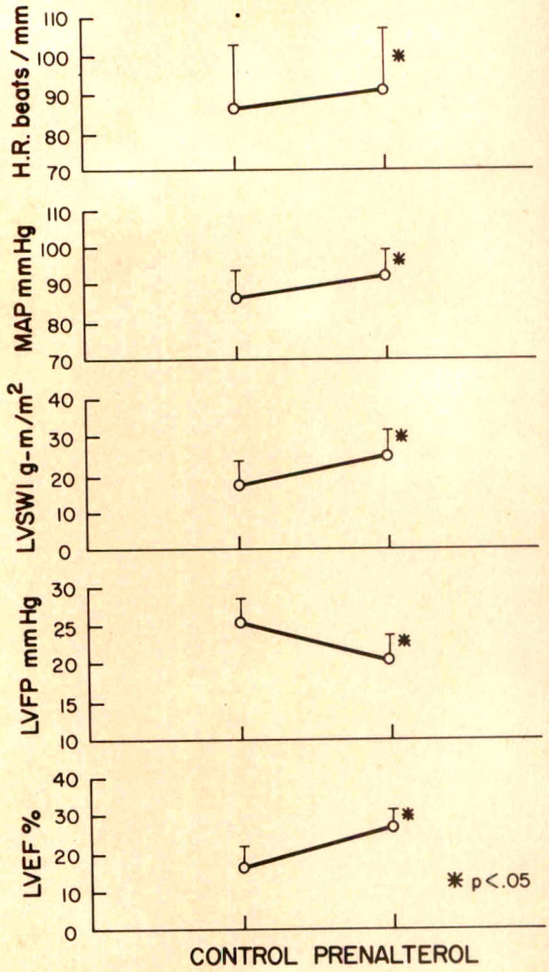

FIGURE 1. Effects of prenalterol on selected hemodynamic variables. Values are expressed as mean ± standard deviation for control state before drug administration and at peak effect. H.R. = heart rate; LVEF = left ventricular ejection fraction; LVFP = left ventricular filling pressure; LVSWI = left ventricular stroke work index; MAP = mean arterial pressure.

The present study demonstrates significant improvement in hemodynamic status after intravenous administration of prenalterol. However, our investigation differs from most previous studies in that only patients with severe low output failure are included. In our study, improved left ventricular performance is demonstrated by statistically significant increases in left ventricular ejection fraction, left ventricular stroke work index and cardiac index. Diminished left ventricular filling pressure may be due to a direct positive inotropic effect resulting in decreased left ventricular end-diastolic volume or due to left ventricular preload reduction from systemic venodilation, or both. The significant reduction in right atrial pressure in our study suggests a systemic venodilating effect. The net hemodynamic effect is a shift in the ventricular function

urve upward and to the left, as found with other inotropic agents. A statistically significant increase in heart ate after prenalterol indicates a residual chronotropic ffect, which may be mediated by stimulation of cardiac eta$_1$ adrenergic receptors affecting heart rate. The ncrease in systolic and mean arterial pressures achieved tatistical significance; however, diastolic arterial ressure did not change significantly. These findings re in agreement with those of previous studies.[4,5] A ecrease in systemic vascular resistance after administration of prenalterol suggests that the increased ystolic and mean arterial pressures are related to increased cardiac contractile force rather than arterial asoconstriction. Significant left ventricular afterload eduction, either by direct beta adrenergic arterial asodilation or by reflex withdrawal of heightened ympathetic vasoconstrictor tone, is a mechanism by hich beta adrenergic stimulants can improve left entricular performance.[22]

Inotropic effect in the presence of myocardial schemia: The decrease in abnormally elevated pulonary vascular resistance after administration of renalterol in this study is comparable with similar hanges noted with dobutamine.[22] There was considrable variation in the patients' response to prenalterol Table I). Although increases in heart rate and systemic ystolic and mean arterial pressure achieved statistical gnificance, it is unlikely that the modest nature of nese changes would be harmful in most patients. In ndividual patients, increased ischemia could result om increases in myocardial oxygen consumption (reected by an increased pressure-rate product) greater nan the increase in blood flow to ischemic tissue caused y beta$_1$ adrenergic stimulation.[23] However, no subctive or objective evidence of aggravated ischemia was resent in this study or that of Ariniego et al.,[5] who valuated prenalterol therapy after recent myocardial nfarction. Similarly, another selective inotropic agent, dobutamine, was not shown to exert an adverse effect on the size of myocardial infarction in experimental animals[24] and in patients.[25]

Prenalterol and ventricular arrhythmia: The only adverse effects found in this study were cardiac arrhythmias. Although catheter-induced arrhythmias or arrhythmias related to the underlying disease cannot be excluded, the temporal association of the arrhythmias with drug administration suggests a causal relation. Ventricular ectopic activity has been observed with other inotropic agents including the catecholamine dobutamine[26] and dopamine,[27] and these agents may have been equally arrhythmogenic in the patients included in this study. Both patients with ventricular tachycardia after administration of prenalterol in this investigation received chronic oral digoxin therapy (with serum levels in the therapeutic range) for ischemic congestive cardiomyopathy after myocardial infarction, raising the possibility that the combination of prenalterol or other adrenergic inotropic agents and digoxin may induce serious ventricular arrhythmias. Increased sympathetic activity has been associated with digitalis toxicity[28] and, conversely, beta adrenergic blockade has been found to be of value in the therapy of digitalis-induced cardiac arrhythmias.[29] Two of our five patients receiving long term oral digoxin therapy did not leave an increase in ventricular ectopic activity. However, the combination of severe ischemic heart failure and previous digoxin therapy appears to warrant particular caution in the administration of prenalterol.

Acknowledgment

We acknowledge the assistance of Steven Hewlett, the nursing staff of the Cardiac Intensive Care Unit and Jean Clare and Kathleen Worthington of the Nuclear Medicine Division, all of the University of Michigan Medical Center. AB Haessle, a division of AB Astra, kindly supplied prenalterol and provided grant support for the study.

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Ventricular Tachycardia: Prediction of Response to Oral Aprindine With Intravenous Aprindine

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Aprindine was administered both intravenously and orally to 25 patients with ventricular tachycardia refractory to conventional antiarrhythmic agents to test the hypothesis that the response to intravenous aprindine predicts the response to oral aprindine. Ten patients had incessant ventricular tachycardia and 15 had paroxysmal sustained inducible ventricular tachycardia.

Eleven patients (43 percent) had conversion to sinus rhythm with intravenous aprindine (nine with incessant and two with paroxysmal sustained ventricular tachycardia). Thirteen patients (all with paroxysmal sustained ventricular tachycardia) manifested slowing of the tachycardia without conversion, whereas in one patient with incessant ventricular tachycardia, the tachycardia became less frequent and nonsustained after intravenous aprindine. All 11 patients who had conversion to sinus rhythm with intravenous aprindine remained free of ventricular tachycardia during oral treatment with aprindine (at 2 weeks) and for a follow-up period of 2 to 38 months (mean 16 ± 13). Of the 14 patients who did not have conversion to sinus rhythm with intravenous aprindine, 12 had spontaneous or inducible ventricular tachycardia, or both, at evaluation 1 to 2 weeks after initiation of oral aprindine.

In conclusion, administration of intravenous aprindine to patients with ventricular tachycardia is helpful in predicting the subsequent response to oral aprindine. In addition, the pattern of ventricular tachycardia predicted the response to aprindine; patients with incessant ventricular tachycardia tended to respond, and those with paroxysmal sustained ventricular tachycardia tended not to respond.

Aprindine is an experimental antiarrhythmic agent useful for management of recurrent drug-resistant ventricular tachycardia. The drug exists for human use as both an intravenous and oral formulation. The half-life of the oral preparation varies from 13 to 50 hours,[1] often necessitating a 1 to 2 week inpatient trial before the efficacy of its oral administration can be adequately assessed. Because of this long trial period, we hypothesized that perhaps the response to intravenous aprindine might predict the response to oral aprindine. If this were the case, then patients could be preselected for oral aprindine therapy based on response to intravenous aprindine, with expectation of cure.

In the present study, we tested the hypothesis that the response to intravenous aprindine predicts the response to oral aprindine. In addition, we also made observations concerning characteristics of ventricular tachycardia that predict a successful response to this antiarrhythmic agent.

Methods

Selection of patients: Criteria for inclusion in this study were as follows: (1) the occurrence of chronic recurrent symptomatic ventricular tachycardia; (2)

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documentation of drug resistance to three or more antiarrhythmic drugs, (procainamide, quinidine, disopyramide or propranolol) as manifested by either the clinical occurrence of ventricular tachycardia during intravenous or oral drug trials, or both, or by the demonstration of laboratory induction of ventricular tachycardia after drug administration[2,3]; (3) the occurrence of spontaneous or induced ventricular tachycardia at a rate and duration suitable for administration of intravenous aprindine, or the occurrence of ventricular tachycardia that was too fast and too poorly tolerated to permit administration of aprindine according to the intravenous protocol (see later), but that was inducible with programmed stimulation, so that intravenous aprindine could be administered just before attempted induction of ventricular tachycardia; and (4) the testing of both intravenous and oral aprindine.

Study patients (Table I): The study group consisted of 25 patients with chronic symptomatic ventricular tachycardia. Their ages ranged from 16 to 69 years (mean 55 ± 14); 20 were male and 5 female. All except 1 patient had organic heart disease; 20 had chronic ischemic heart disease (all with remote infarction more than 3 weeks before the initial onset of ventricular tachycardia), 3 had primary myocardial disease (congestive cardiomyopathy) and 1 had hypertensive cardiovascular disease.

Characteristics of ventricular tachycardia: Patients could be categorized on the basis of the pattern of occurrence of ventricular tachycardia (Table I). Patients 1 to 15 had sporadic paroxysmal sustained ventricular tachycardia. These patients were afflicted with sustained and persistent attacks of ventricular tachycardia, necessitating conversion either electrically or with parenteral medication, or both. The frequency of occurrence of ventricular tachycardia ranged from 3 to 20 attacks/year (mean 7 ± 5). The ventricular tachycardia rates ranged from 140 to 260 beats/min (mean 188 ± 37). The QRS complex during ventricular tachycardia had a right bundle branch block pattern in 11 patients (7 patients with left and 4 with right axis deviation), and a left bundle branch block pattern in the remaining 4 patients (all with left axis deviation). Ventricular tachycardia was inducible by programmed electrical stimulation in all of these patients.

Ten patients (Patients 16 to 25) could be categorized by the presence of incessant ventricular tachycardia. In these patients, the control state (without medication) was usually characterized by persistent ventricular tachycardia, either sustained or nonsustained (episodes of ventricular tachycardia interrupted by short periods of normal sinus rhythm). The duration of the episode or episodes of incessant ventricular tachycardia before testing with intravenous aprindine ranged

TABLE I

Clinical and Electrocardiographic Findings

Case	Age (yr) & Sex	Diagnosis	ECG QRS Configuration	Ventricular Tachycardia			
				Rate (beats/min)	QRS Configuration	Frequency (attacks/yr) or Duration (days)	Inducible
			Paroxysmal Sustained Ventricular Tachycardia				
1	60M	ASHD	AWMI, LAHB	160	RBBB, RAD	4/yr	Yes
2	20F	PMD	Normal	190	RBBB, LAD	6/yr	Yes
3	60M	ASHD	IWMI	230	RBBB, LAD	4/yr	Yes
4	58M	ASHD	IWMI	180	RBBB, LAD	15/yr	Yes
5	69F	ASHD	AWMI	170	LBBB, LAD	9/yr	Yes
6	53M	ASHD	IWMI	140	RBBB, LAD	6/yr	Yes
7	16F	...	Normal	260	LBBB, LAD	4/yr	Yes
8	59M	ASHD	AWMI, LAHB	190	RBBB, RAD	5/yr	Yes
9	58M	ASHD	LBBB	140	RBBB, RAD	4/yr	Yes
10	69F	ASHD	IWMI	250	RBBB, LAD	4/yr	Yes
11	43M	ASHD	IWMI	150	LBBB, LAD	20/yr	Yes
12	62M	ASHD	AWMI	165	LBBB, LAD	10/yr	Yes
13	50M	HCVD	LBBB	210	RBBB, LAD	5/yr	Yes
14	63M	ASHD	LVH	190	RBBB, RAD	4/yr	Yes
15	61M	ASHD	LBBB	200	RBBB, LAD	3/yr	Yes
			Incessant Ventricular Tachycardia				
16	65M	ASHD	LBBB	150	RBBB, LAD	2 days	...
17	60M	ASHD	AWMI, IWMI RBBB, LAHB	165	LBBB, LAD	3 days	...
18	68M	ASHD	IWMI	160	LBBB, LAD	0.16 day	...
19	58M	PMD	RBBB, LAHB	125	LBBB, LAD	15 days	...
20	61M	ASHD	LAHB	150	RBBB, RAD	1 day	...
21	46M	ASHD	IWMI	170	LBBB, LAD	13 days	...
22	52M	PMD	LAHB	165	LBBB, RAD	6 days	...
23	62M	ASHD	AWMI	205	RBBB, RAD	1 day	...
24	65F	ASHD	LBBB	165	LBBB, RAD	3 days	...
25	34M	ASHD	AWMI	160	RBBB, LAD	8 days	...

ASHD = atherosclerotic heart disease; AWMI = anterior wall myocardial infarction; ECG = electrocardiographic; HCVD = hypertensive cardiovascular disease; IWMI = inferior wall myocardial infarction; LAD = left axis deviation; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; PMD = primary myocardial disease, RAD = right axis deviation; RBBB = right bundle branch block.

TABLE II

Effects of Intravenous and Oral Aprindine

	Intravenous Aprindine			Oral Aprindine (1 to 2 weeks)			
Case	Initial VT Rate (beats/min)	Response; VT Rate (beats/min)	Dose at Conversion (mg)	Dose/Day (mg)	Response	Rate (beats/min)	Results of Long-term Aprindine Follow-Up
1	160	Slowing, 130	. . .	100	No VT	. . .	9 months (NSR)
2	190	Slowing, 150	. . .	200	No VT	. . .	2 months (NSR)
3	230	Slowing, 170	. . .	200	Inducible VT	100	. . .
4	180	Slowing, 150	. . .	100	Inducible VT	170	. . .
5	175	Slowing, 135	. . .	200	Inducible VT	150	. . .
6	140	Slowing, 120	. . .	200	Inducible VT	175	. . .
7	260	Slowing, 210	. . .	200	Inducible VT	145	. . .
8	200	Slowing, 160	. . .	200	Inducible VT	135	Death at 1 month
9	165	Slowing, 120	. . .	200	Inducible VT	125	50 months (VT)
10	240	Slowing, 200	. . .	200	Inducible VT	180	. . .
11	150	Slowing, 115	. . .	225	Inducible VT	115	. . .
12	165	Slowing, 145	. . .	225	Inducible VT	140	. . .
13	170	CNSR	150	100	No VT	. . .	37 months (NSR)
14	190	CNSR	25	75	No VT	. . .	17 months (NSR)
15	200	Slowing, 155	. . .	200	Inducible VT	140	. . .
16	150	CNSR	150	110	No VT	. . .	16 months (NSR)
17	150	CNSR	75	150	No VT	. . .	10 months (NSR)
18	200	CNSR	200	125	No VT	. . .	8 months (NSR)
19	125	CNSR	150	150	No VT	. . .	38 months (NSR)
20	140	CNSR	200	100	No VT	. . .	4 months (NSR)
21	165	CNSR	100	200	No VT	. . .	17 months (NSR)
22	170	CNSR	150	175	No VT	. . .	21 months (NSR)
23	205	CNSR	200	150	No VT	. . .	2 months (NSR)
24	165	CNSR	100	100	No VT	. . .	1 month (NSR)
25	160	Nonsustained VT (less frequent)	. . .	300	Inducible VT	150	. . .

CNSR = conversion to normal sinus rhythm; NSR = normal sinus rhythm; VT = ventricular tachycardia.

from 4 hours to 15 days (mean 5 ± 5 days). The rates of the tachycardia ranged from 125 to 205 beats/min (mean 160 ± 21). The QRS complex during ventricular tachycardia had a right bundle branch block pattern in four patients (two with left and two with right axis deviation) and a left bundle branch block pattern in six (four with left and two with right axis deviation).

Aprindine protocol and follow-up: In 20 patients (10 with sporadic and 10 with incessant paroxysmal sustained ventricular tachycardia), intravenous aprindine was administered during ventricular tachycardia with an infusion rate of 5 mg/min to a total dose of 200 mg over 40 minutes. In five patients (Cases 3, 7, 8, 10 and 15) with paroxysmal sustained ventricular tachycardia, the rate of ventricular tachycardia was too fast to tolerate the 40 minute infusion, so that 200 mg of aprindine was administered during sinus rhythm (5 mg/min for 40 minutes) immediately before attempted induction of ventricular tachycardia. Oral aprindine was administered in

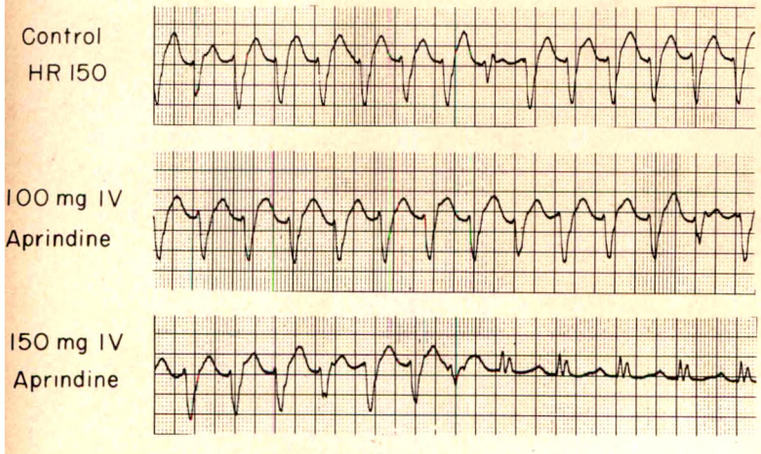

FIGURE 1. Conversion of ventricular tachycardia to normal sinus rhythm with intravenous (IV) aprindine in a patient with incessant ventricular tachycardia. HR = heart rate (beats/min).

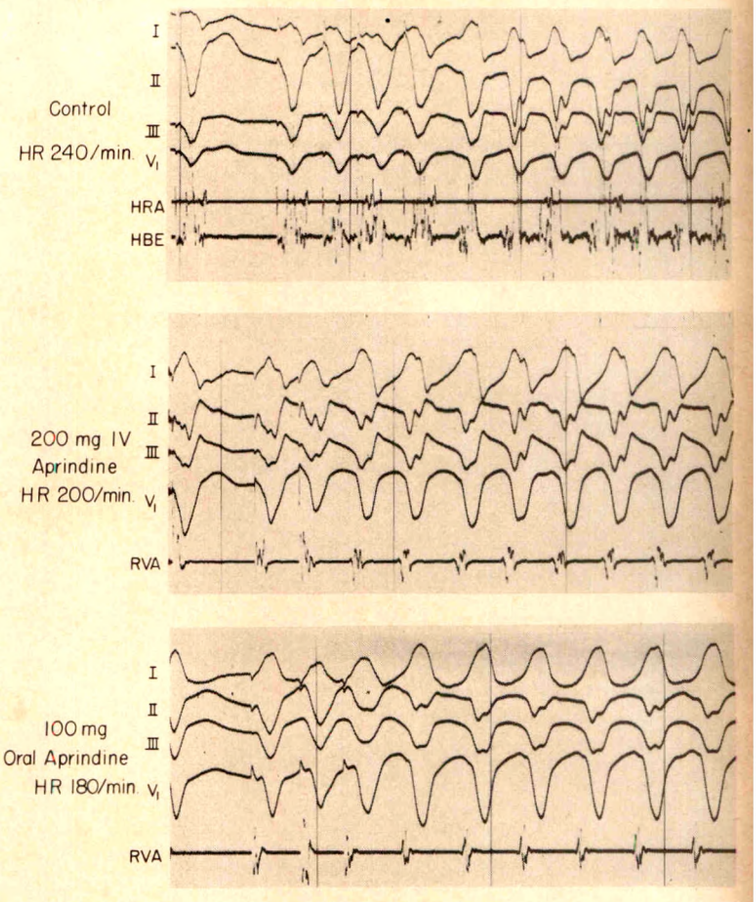

FIGURE 2. Slowing of induced ventricular tachycardia with intravenous (IV) and oral aprindine. Each panel demonstrates ventricular extra-stimulus induction of sustained ventricular tachycardia. No conversion to sinus rhythm was observed. HBE = His bundle electrogram; HR = heart rate (beats/min); HRA = high right atrium; RVA = right ventricular apex.

a daily dose of 100 to 300 mg with the dose adjusted depending on the occurrence of neurotoxicity. Inpatient monitoring was utilized during the initial oral drug trial. Outpatient follow-up study was instituted in appropriate patients in our arrhythmia clinic (see later).

Cure of ventricular tachycardia was defined by the absence of ventricular tachycardia with prolonged inpatient and outpatient monitoring in the patients with incessant ventricular tachycardia, or by inability to induce ventricular tachycardia with electrophysiologic studies as well as lack of recurrence of arrhythmia in the patients with paroxysmal sustained ventricular tachycardia. Statistical analyses were performed utilizing the chi-square test.

Results

Intravenous aprindine (Table II): Intravenous aprindine resulted in conversion to normal sinus rhythm in 11 (44 percent) of the 25 patients. Of these 11 patients, 9 (Cases 16 to 24) had incessant and 2 (Cases 13 and 14) had paroxysmal sustained ventricular tachycardia. In the latter two, aprindine was given during an induced attack in the first patient and during a spontaneous attack in the second. These 11 patients had conversion at a dose of 25 to 200 mg (mean 134 ± 58) of intravenous aprindine. In all 11 conversion of ventricular tachycardia was preceded by a slowing of ventricular rate (Fig. 1).

Intravenous aprindine failed to convert ventricular tachycardia in 14 patients (56 percent) (Cases 1 to 12, 15 and 25). Slowing of induced or spontaneous ventricular tachycardia without conversion to sinus rhythm was seen in 13 of these patients (Fig. 2). In these patients ventricular rate was slowed by 20 to 60 beats/min (mean 39 ± 12) with a resulting mean rate of ventricular tachycardia of 190 beats/min before and 151 beats/min after intravenous aprindine. In one patient (Case 25) with incessant ventricular tachycardia, the tachycardia became less incessant but did not slow.

Oral aprindine at 1 to 2 weeks (Table II): The nine patients with incessant ventricular tachycardia who had conversion to sinus rhythm with intravenous aprindine were monitored, and no recurrence of ventricular tachycardia was noted at 2 weeks. In one patient (Case 13) with paroxysmal sustained ventricular tachycardia who had conversion to sinus rhythm with intravenous aprindine, an electrophysiologic study 2 weeks after oral aprindine demonstrated inability to induce ventricular tachycardia. One patient (Case 14) was not studied at 1 to 2 weeks but was started on long-term oral aprindine therapy (see later).

The 13 patients with slowing of ventricular tachycardia without conversion to sinus rhythm after intravenous aprindine (Cases 1 to 12 and 15) were restudied

1 to 2 weeks after initiation of oral aprindine therapy. Eleven patients had inducible ventricular tachycardia (Fig. 2), whereas in two patients (Cases 1 and 2) ventricular tachycardia was no longer inducible. The patient (Case 25) with incessant ventricular tachycardia (not responding to intravenous aprindine) had spontaneous and inducible ventricular tachycardia at 2 weeks.

Long-term oral aprindine (Table II): Follow-up of the 11 patients who had conversion to normal sinus rhythm with intravenous aprindine revealed that all had cure of ventricular tachycardia with oral aprindine. Nine of these patients (Cases 16 to 24) had incessant ventricular tachycardia. These nine were cured with oral aprindine therapy with a follow-up period of 1 to 38 months (mean 13 ± 12). Two patients (Cases 13 and 14) who had conversion to sinus rhythm with intravenous aprindine had paroxysmal sustained ventricular tachycardia with a frequency of 5 and 4 attacks/year, respectively, before the aprindine trial. Both patients were cured with oral aprindine, with no recurrence of ventricular tachycardia over a follow-up period of 37 and 17 months, respectively.

Two patients (Cases 1 and 2) with paroxysmal sustained ventricular tachycardia whose tachycardia slowed without conversion to sinus rhythm with intravenous aprindine but was not inducible after 2 weeks of oral aprindine therapy were followed up for 2 and 9 months, respectively, on oral aprindine therapy without recurrence of ventricular tachycardia.

Aprindine was discontinued in all but two of the remaining patients because of failure to achieve sinus rhythm at initial study and at 1 to 2 weeks (see earlier). Aprindine was administered chronically in two patients despite lack of successful response (Cases 8 and 9) because no other available therapy seemed preferable. Recurrent ventricular tachycardia developed in one of these patients (Case 9) despite aprindine, and one died (Case 8) approximately 1 month after initiation of oral aprindine.

Prediction of cure with oral aprindine (Fig. 3): The response to intravenous aprindine was an excellent predictor of the response to oral aprindine. All 11 patients who had conversion to sinus rhythm with intravenous aprindine were subsequently cured with oral aprindine, whereas only 2 of 14 patients who did not have conversion to sinus rhythm were cured with oral aprindine ($p < 0.001$). The response to intravenous aprindine predicted 11 of 13 possible cures (85 percent).

The pattern of ventricular tachycardia also predicted cure with oral (and intravenous) aprindine. Nine of 10 patients with incessant ventricular tachycardia were cured with oral aprindine compared with only 4 of 15 patients with paroxysmal sustained ventricular tachycardia ($p < 0.005$). Thus, the presence of incessant ventricular tachycardia predicted 9 of 13 possible cures.

Adverse effects: Twelve of the 25 patients manifested mild neurotoxicity after the oral dose of aprindine was established (7 with paroxysmal sustained and 5 with incessant ventricular tachycardia). The neurotoxicity consisted primarily of mild tremor or mild ataxia, or both. No patient manifested clinically significant aprindine hepatitis or agranulocytosis.

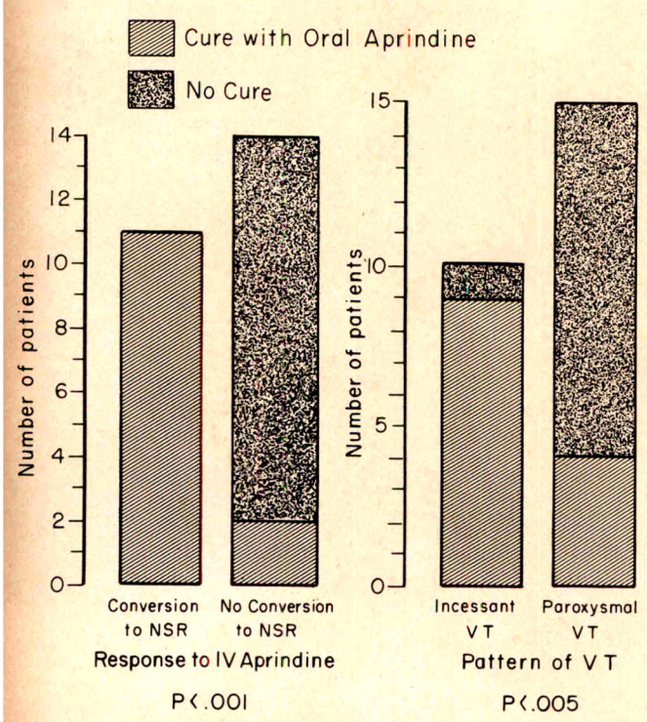

FIGURE 3. Prediction of cure of ventricular tachycardia according to response to intravenous (IV) aprindine (**left panel**) and pattern of ventricular tachycardia (VT) (**right panel**). See text for discussion. NSR = normal sinus rhythm.

Discussion

Aprindine is a potent antiarrhythmic agent currently available for use in Europe and now undergoing clinical investigation in the United States. One of the characteristics of aprindine is its long half-life of 13 to 50 hours[1]; therefore oral clinical trials of at least 1 week are necessary to reach full antiarrhythmic efficacy. The drug is well absorbed when given orally, and approximately 95 percent of the hydroxylated metabolites of aprindine undergo glucuronidation in the liver; 65 percent of the drug and its metabolites appear in small concentration in the plasma of patients on long-term therapy.[1,4]

Previous experience with aprindine: Aprindine has been used successfully in patients with a variety of supraventricular and ventricular arrhythmias.[5–10] Zipes et al.[6] recently emphasized its usefulness in refractory cases of supraventricular tachycardia incorporating accessory pathways (Wolff-Parkinson-White syndrome). Fasola et al.[11] reported on 23 patients with re-

current drug-resistant ventricular tachycardia and fibrillation; most of these patients had old myocardial infarction. After administration of aprindine no patient with ventricular fibrillation had recurrence of arrhythmia, and ventricular tachycardia was abolished in all but five patients; in three of the latter five patients ventricular tachycardia was of very short duration and slow rate, so that discontinuation of the drug was not necessary.

Wei et al.[12] described 10 patients with mitral valve prolapse and drug-refractory ventricular tachycardia; 4 of these patients had a history of ventricular fibrillation. In all 10 patients ventricular tachycardia was no longer observed after administration of aprindine. Additionally, 9 of the 10 patients had a 40 percent or greater reduction in the frequency of ventricular premature complexes. Troup and Zipes[13] also reported on seven patients with mitral valve prolapse and recurrent drug-refractory ventricular tachycardia. In all patients, ventricular tachycardia was abolished during long-term aprindine therapy and a 91 percent reduction was observed in the total number of premature ventricular complexes per 24 hours.

Intravenous versus oral aprindine: Because of the long half-life of aprindine, a 1 to 2 week oral trial is necessary to determine clinical efficacy. A similar response of arrhythmia to both intravenous and oral aprindine would be of great clinical significance, because the intravenous response can be obtained in one relatively short testing period.

In most previous reports, aprindine was administrated intravenously or orally, or both, but not systematically to all patients by both routes. In the present study, our overall rate of success was 52 percent (13 of 25 patients), which is an acceptable rate considering that all of these patients were refractory to conventional antiarrhythmic agents. Patients who did not have conversion to sinus rhythm with intravenous aprindine manifested a reduction either in rate (13 patients) or in frequency (1 patient) of ventricular tachycardia (Fig. 2). Both of these responses improved the patient's hemodynamic status; thus in two patients in whom no other modality of therapy was available, aprindine was given as long-term oral therapy. The majority of patients receiving long-term oral therapy manifested adverse central nervous system effects, but in all patients a dose was achieved whereby these effects, if any, were well tolerated and cure of ventricular tachycardia was still present.

Eleven patients who had conversion to sinus rhythm with intravenous aprindine were subsequently cured with oral aprindine, whereas 2 of 14 patients who did not have conversion with intravenous aprindine were subsequently cured with oral aprindine. Intravenous aprindine predicted 83 percent of the cures (Fig. 3, left panel). Nine of the 11 patients who had conversion to sinus rhythm with intravenous aprindine had incessant ventricular tachycardia (9 of the 10 patients with incessant ventricular tachycardia). Only 2 of the 11 patients who had conversion to sinus rhythm with intravenous aprindine had paroxysmal sustained ventricular tachycardia, and only 4 of the 15 patients with paroxysmal sustained ventricular tachycardia were cured with oral aprindine (Fig. 3, right panel).

The explanation for these responses deserves some comment. It is not surprising that the response to intravenous aprindine predicts the response to oral aprindine because in our experience, electrophysiologic testing of intravenous drugs in patients with paroxysmal supraventricular tachycardia often predicts the response to oral agents.[3] It is not clear why, in the present study, occasionally responses were achieved with oral aprindine that were not achieved with intravenous aprindine. In these instances, the tissue drug level achieved with oral loading for 1 to 2 weeks may be greater than that achieved with intravenous loading.

It is not clear why patients with incessant ventricular tachycardia tend to respond to aprindine, whereas those with paroxysmal sustained ventricular tachycardia do not. The pathophysiologic characteristics of the former arrhythmia are not clear to us, whereas the latter appears to be reentrant (using commonly accepted criteria). Until the pathophysiologic features of ventricular tachycardia and the pharmacologic features of aprindine are further elucidated, the answers to these questions will probably remain elusive.

Clinical implication: Our study suggests several conclusions. Administration of intravenous aprindine to patients with ventricular tachycardia is helpful in predicting the subsequent response to oral aprindine. Specifically, conversion of ventricular tachycardia to sinus rhythm with intravenous aprindine predicts cure of ventricular tachycardia with oral aprindine. Failure of conversion with intravenous aprindine usually predicts failure of therapy with oral aprindine.

The pattern of ventricular tachycardia is also useful in predicting the response to both intravenous and oral aprindine. Patients with incessant ventricular tachycardia are likely to have conversion to normal sinus rhythm with intravenous aprindine and have permanent conversion with oral aprindine. In contrast, in patients with paroxysmal sustained ventricular tachycardia a favorable response to either intravenous or oral aprindine is unusual. It is our opinion that administration of intravenous aprindine should be utilized as a test before embarking on oral aprindine therapy in patients with recurrent ventricular tachycardia. Since a few patients respond successfully only to oral (and not to intravenous) administration of aprindine, oral aprindine can be given to patients with ventricular tachycardia who do not respond to intravenous aprindine. However, in the latter situation, cure with oral aprindine therapy will usually not be achieved.

Acknowledgment

We thank Frances Jefferson for her excellent secretarial help.

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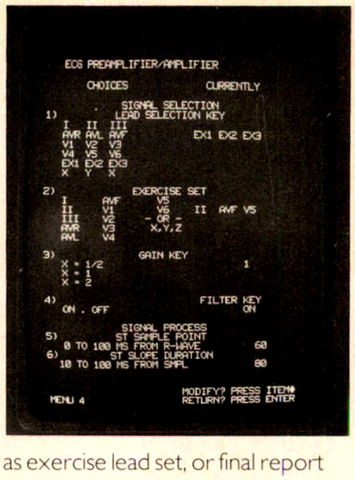

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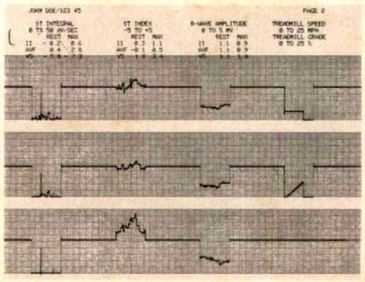

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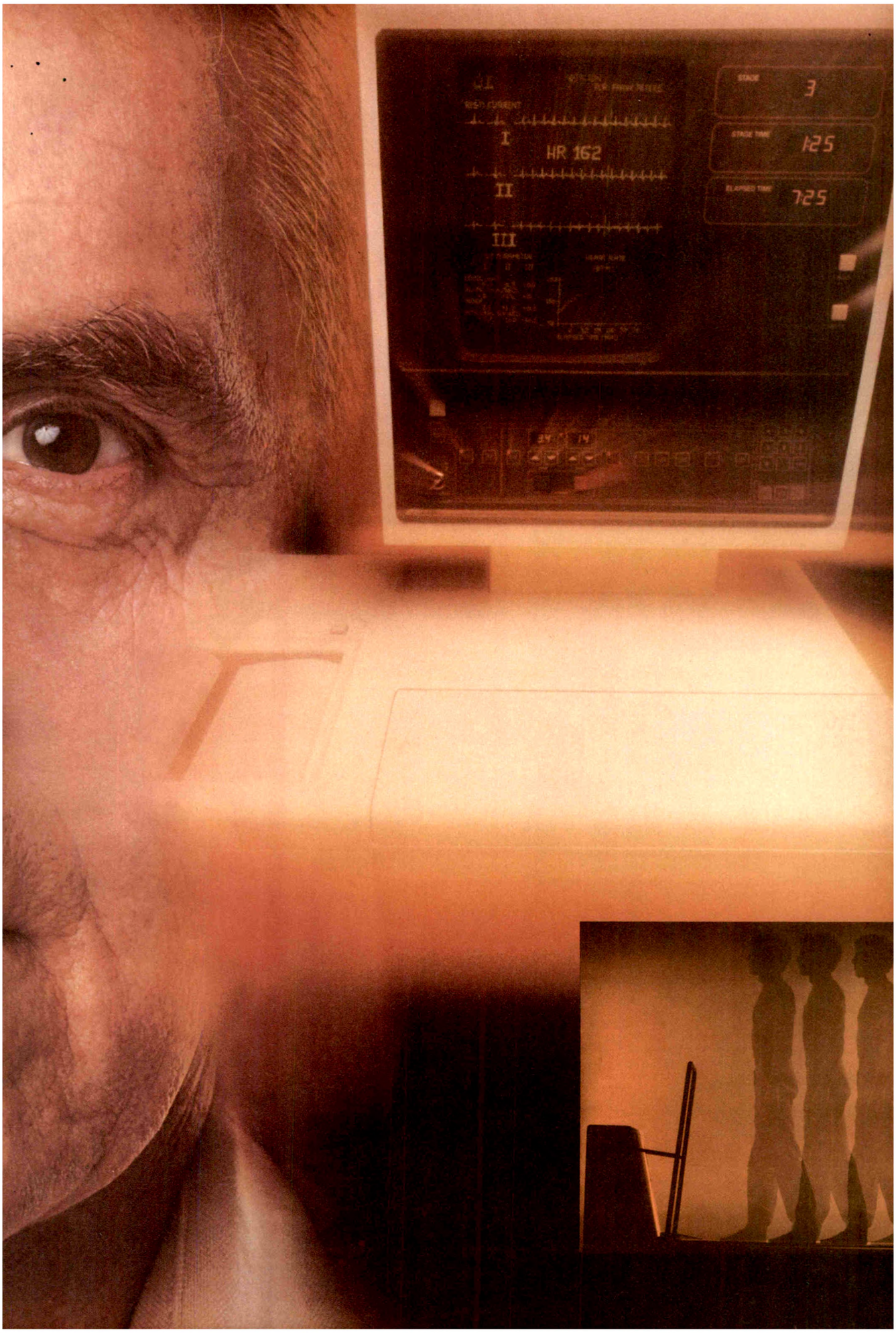
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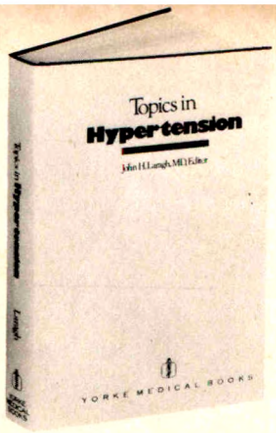

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PARTICIPANTS:

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Dennis Krikler, M.D., F.A.C.C.
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SUMMARY STATEMENT: **Dennis Krikler, M.D., F.A.C.C.**

Richard A. Matthay, MD and Lawrence D. H. Wood, MD, Guest Editors

Introduction: The Functionally Integrated Cardiovascular-Pulmonary Unit

RICHARD A. MATTHAY, MD
LAWRENCE D. H. WOOD, MD

New Haven, Connecticut
Winnipeg, Manitoba, Canada

Respiratory failure is usually defined on the basis of alterations in arterial blood gas composition: an arterial oxygen tension less than 60 mm Hg or an arterial carbon dioxide tension greater than 50 mm Hg, or both. Abnormalities leading to respiratory failure are multiple, ranging from disturbances in the control of breathing (for example, drug overdose) to impaired function of the airways (acute bronchial asthma) to disorders of the lung parenchyma (pneumonia).[1] A major goal in the treatment of patients with respiratory failure has been to provide adequate tissue oxygenation. Oxygen delivery to tissues is the product of blood oxygen content and cardiac output. Until recently, patients with acute respiratory failure, particularly those with the adult respiratory distress syndrome, died rapidly of hypoxemia with markedly depressed arterial and venous oxygen contents and severe venous admixture. However, advances in respiratory care, including mechanical ventilation with positive end-expiratory pressure, have reversed hypoxemia and have extended the life span of patients with acute respiratory failure.[2,3] Thus, patients who reach an intensive care unit now seldom die simply of hypoxemia.[4]

Yet, mortality from respiratory failure remains high. Between 1973 and 1976, the mortality rate from adult respiratory distress syndrome at San Francisco General Hospital was 53 percent.[1] At the Beth Israel Hospital in Boston, among all patients who required mechanical ventilation due to respiratory failure the mortality rate was approximately 20 percent.[5] Clearly other factors than hypoxemia, which can now be corrected in most patients, must be contributing to mortality in patients with respiratory failure.[1,2,4]

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Recently, marked abnormalities in cardiovascular function have been identified in patients with both acute and chronic respiratory failure, and each of these abnormalities may have adverse effects on tissue oxygen delivery and on patient outcome. Among these cardiovascular disturbances are pulmonary arterial hypertension and elevated pulmonary vascular resistance, depressed right and left ventricular performance, and reduced cardiac output.[2,4–13] Intrathoracic pressure changes,[13,14] which occur in acute and chronic respiratory insufficiency, may affect myocardial pump performance, blood return to the right heart chambers, cardiac output and, hence, oxygen delivery to tissue. Moreover, it is now evident that mechanically assisted ventilation and positive end-expiratory pressure may exert adverse effects on the cardiovascular system[7,11,13–15] while simultaneously improving arterial oxygen tension and content in acute respiratory failure. Correcting arterial hypoxemia alone may be inadequate, and methods utilized to improve arterial oxygenation may adversely affect the cardiovascular system and ultimately patient survival. Accordingly, in treating patients with respiratory insufficiency, it is imperative to consider the heart and lungs together as a functionally interrelated cardiovascular-pulmonary unit. Evolving appreciation of this concept formed the basis of the reports[16–20] in this Seminar, which reviews the relation among systemic vessels, the heart and the lungs in acute and chronic respiratory failure.

Contractile Mechanics and Interaction of the Right and Left Ventricles

The first paper of the Seminar[16] discusses myocardial contractile mechanics and the interrelation between the right and left ventricles within the context of the functional cardiopulmonary unit. As Weber et al.[16] describe it, the cardiopulmonary unit consists of three anatomic subunits: "two in-series muscle pumps, the right and left heart chambers, which are mechanically coupled by the lungs." The anatomic arrangement and mechanical

interaction of these three subunits facilitate their functional integration. Thus, the interventricular septum and the pericardium promote interaction between ventricles, while intrathoracic pressure or pleural pressure envelops the entire unit, creating an additional interaction between the ventricles and the heart and lungs.

Viewing the heart as an integral part of the cardiopulmonary unit, Weber et al. review three aspects of myocardial mechanics: (1) the concept of wall force and stress, (2) the isovolumetrically beating ventricle, and (3) the ejecting ventricle. They present data from studies with the isolated heart preparation that show interaction between the right and left ventricles during both diastole and systole. Moreover, the position and motion of the interventricular septum, regulated by the transseptal force gradient, is shown to be critical in determing this interaction. Finally, they discuss the influence of both intrapericardial and intrathoracic pressures on transmural pressure and thus on myocardial function. Respiratory failure is associated frequently with stiff lungs and requirement for mechanical ventilation, both of which can cause marked swings in intrathoracic pressure and transmural pressures. In such a setting, effects on myocardial pumping function may be dramatic.

Role of Systemic Vessels in Control of Cardiac Output

In the next paper, Goldberg and Rabson[17] review determinants of venous flow to the heart: (1) mean pressure in the systemic vasculature, (2) right atrial pressure, and (3) resistance to venous return. Although these concepts have previously been elucidated, they have not received considerable clinical attention in the setting of respiratory failure. The major focus has been directed toward cardiovascular disturbances in respiratory failure in which the heart is damaged and itself limits cardiac output. However, in patients with acute or chronic respiratory failure without cardiac dysfunction, factors governing venous return may be important in causing disturbances of cardiovascular function. Moreover, as Goldberg and Rabson indicate, several therapeutic modalities employed in respiratory failure may affect the relation between mean systemic pressure and right atrial pressure, thereby altering venous return to the heart and cardiac output.[17] Some of these modalities include positive pressure (mechanical) ventilation, diuretics, cardiac glycosides and other inotropic or vasoactive drugs.

Cardiovascular Disturbances in Chronic Respiratory Insufficiency

In the third paper, Robotham[18] applies the physiologic concepts of the functional cardiopulmonary unit and venous return discussed in the first two papers[16,17] to patients with chronic respiratory insufficiency. How mechanical factors in chronic respiratory insufficiency influence right and left ventricular performance, venous return and cardiac output during both spontaneous and mechanical ventilation is discussed. Further, Robotham reviews several factors present during intermittent positive pressure ventilation that act together to improve left ventricular performance in respiratory failure despite concomitant adverse effects on right ventricular performance.

Noninvasive Radiographic Assessment of Cardiovascular Functions in Acute and Chronic Respiratory Failure

In the fourth paper of this Seminar Berger and Matthay[19] critically review recent advances in noninvasive assessment of cardiovascular performance in respiratory failure. They discuss three noninvasive modalities for evaluating the cardiovasculature: (1) the plain chest radiograph, (2) radionuclide imaging, and (3) echocardiography. Moreover, they present data establishing the clinical applicability of these techniques in patients with acute and chronic respiratory failure. Their data demonstrate the ability of radionuclide angiocardiography (1) to detect clinically inapparent right and left ventricular performance abnormalities, and (2) to detect alterations in biventricular performance after therapeutic intervention in patients with respiratory failure.

Cardiovascular Management in Acute Hypoxemic Respiratory Failure

The last paper attempts to apply the concepts and methodologies described in previous seminar papers to the clinical problems of low pressure pulmonary edema. Wood and Prewitt[20] review aspects of the treatment of cardiogenic pulmonary edema in which classic therapeutic aims are to lower pulmonary vascular pressures and to increase cardiac output. They extend these principles to low pressure edema, in which small reductions in pulmonary wedge pressure reduce edema, yet similar increases in circulating colloid osmotic pressure do not. They propose a therapeutic goal of the lowest pulmonary wedge pressure consistent with adequate cardiac output, using colloid to maintain sufficient circulating volume but not to reduce edema. When cardiac output becomes insufficient as pulmonary wedge pressure is reduced, vasoactive agents may be used to return cardiac output to normal without increasing wedge pressure or edema. Their review of the effects of vasoactive agents on pulmonary oxygen exchange suggests that pulmonary vasoactivity of these drugs does not increase shunt. Further, they conclude that positive end-expiratory pressure does not depress ventricular function.

Because positive end-expiratory pressure reduces pulmonary shunt by redistributing but not reducing pulmonary edema, they contend that the least positive end-expiratory pressure required to achieve 90 percent oxygen saturation of an adequate circulating hemoglobin on a nontoxic inspired oxygen concentration is a reasonable therapeutic objective. Finally, they emphasize that many of their conclusions are based on

canine data requiring clinical trials for validation, and they point out that many investigative methods described in previous Seminar papers are now available to test such therapeutic hypotheses.

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Part II of this Seminar will appear in the April 1981 issue of the Journal.

Contractile Mechanics and Interaction of the Right and Left Ventricles

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The heart and lungs, together with hemoglobin, provide for the transport of oxygen from the atmosphere to the metabolizing tissue. The oxygenation of blood and the circulation of oxygenated blood are precisely synchronized so that the heart and lungs constitute an integrated cardiopulmonary unit. The functional integration of the heart and lungs is fostered by their anatomic arrangement and mechanical interaction.

The cardiopulmonary unit consists of the right and left ventricles (two in-series pumps composed of cardiac muscle), which are mechanically coupled by the lungs. The factors that control cardiac muscle shortening (fiber length, afterload and myocardial contractile state) also regulate the pumping behavior of each ventricle. Because the ventricles are aligned in series a perturbation in the mechanical events of one ventricle will influence the behavior of the other ventricle. The interventricular septum and pericardium further promote the mechanical interplay between ventricles. Intrathoracic pressure (the pressure that surrounds the cardiopulmonary unit) creates an additional interaction between the ventricles as well as the heart and lungs.

The heart and lungs, together with hemoglobin, provide for the transport of oxygen from the atmosphere to the metabolizing tissues. Normally, the oxygenation of blood and the circulation of oxygenated blood are precisely synchronized so that the heart and lungs constitute a functionally integrated cardiopulmonary unit designed for oxygen transport.

This cardiopulmonary unit consists of three anatomic subunits: two in-series muscle pumps, the right and left ventricles, which are mechanically coupled by the lungs (Fig. 1). The functional integration of these subunits is fostered by their anatomic arrangement and mechanical interaction. The mobile interventricular septum and pericardium promote the interaction between ventricles, while intrathoracic or pleural pressure surrounds the entire unit and creates a second interaction between the ventricles as well as the heart and lungs. It will be the purpose of this review to consider specifically the contractile mechanics and interaction of the two pumps and their integration within the cardiopulmonary oxygen transport unit. An understanding of the physiologic behavior of the cardiopulmonary unit will provide critical insight into the clinical recognition and management of the patient with respiratory failure.

The Heart As a Muscular Pump

The myocardium is a syncytium of muscle fibers tethered within a supportive network of collagen. The contraction or shortening of these muscle fibers results in the generation of pressure within the ventricular chambers, thickening of the wall and a reduction in ventricular volume. The factors that control muscle fiber shortening also control the pumping behavior of the ventricle and, hence, we may view the heart as a muscular pump.[1]

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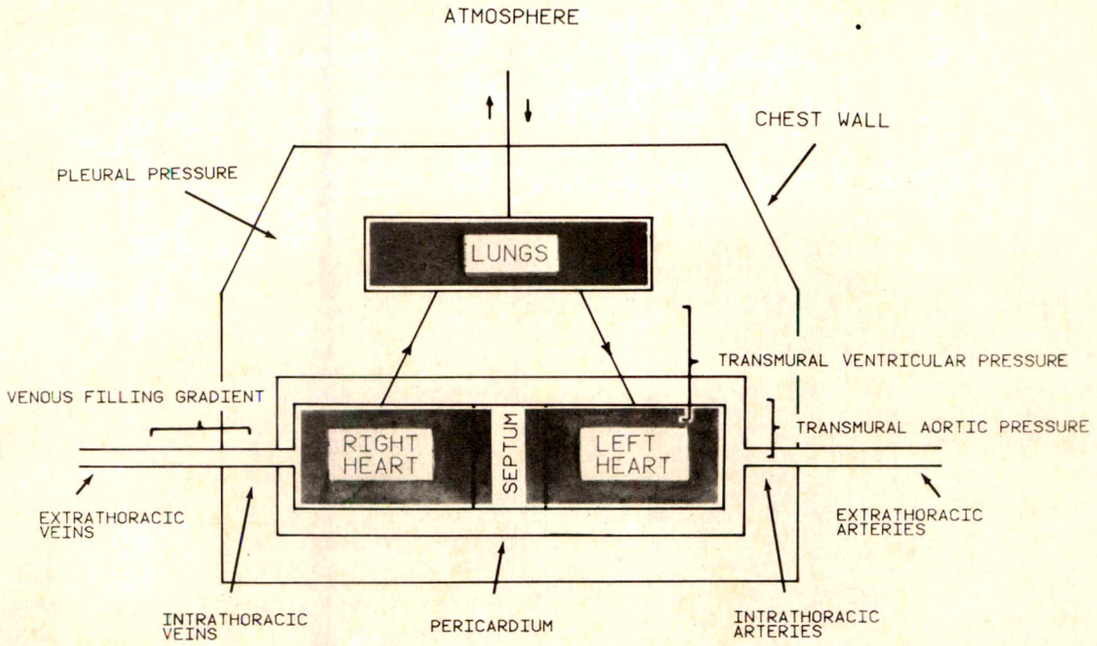

FIGURE 1. The cardiopulmonary unit consists of the right and left heart chambers mechanically coupled by the lungs and enclosed within the thorax. The pericardium, interventricular septum and pleural pressure contribute to the mechanical interaction of the two ventricles and the heart and lungs.

The Concept of Wall Force and Stress

Wall force: In isolated cardiac muscle it is well known that muscle length and muscle shortening are a function of the external force that exists on the muscle before and during its contraction, respectively. In the intact heart in which the arrangement of muscle fibers is complex, an approximation of force is needed; *however, ventricular pressure alone is not an adequate description of force.* A net *force* (grams) existing across the myocardial wall in any particular plane can be derived from the product of chamber pressure (g/cm^2) and the cross-sectional area (cm^2) of the chamber included in the plane.[1,2] The load on the muscular wall and its muscle fibers therefore is a function of both chamber pressure and the configuration of the chamber. As a case in point, the myocardium surrounding the enlarged ventricle has to develop more force to generate a given level of pressure than does the normal-sized heart. In similar fashion the force that exists at the apex of the ventricle will be less than that along its equator.

Wall stress: Force per unit of cross-sectional area of the myocardium (g/cm^2) represents wall *stress.* Wall thickness is presumed to be a function of regional wall force[3]; hence, stress is homogeneously distributed throughout the ventricle (for example, the smaller force at the apex is distributed over a thinner area of myocardium), thereby favoring uniform wall motion.

One would also predict that stress is uniformly distributed across the interventricular septum. However, septal stress will be a function of the right and left ventricular forces acting on the septal surfaces. A marked gradient in transseptal surface forces would promote a shift of the septum to the chamber with less force and potentially obliterate this ventricle (Fig. 2). As is the case with the free wall of either ventricle, it is not satisfactory to consider pressure or the gradient in pressure across the septum as the sole factor regulating its position. For example, the systolic pressure in the left ventricle is normally five times that in the right ventricle and yet the integrity of the right ventricular chamber is maintained. However, an acute increase in chamber size, such as may occur in the right ventricle with marked negative intrathoracic pressure, will induce a gradient and shift the septum toward the left ventricle (Fig. 2). Septal displacement, which occurs as a result of the disturbance in the transseptal gradient in force, will also be accompanied by changes in shape and size of each ventricle and their effective compliance. For example, a leftward shift of the septum (that is, toward the left ventricle) decreases the septal to left ventricular free wall dimension while increasing the anteroposterior dimension (Fig. 2). This alteration in chamber configuration contributes to the change in filling volume and pressure (distensibility) associated with fluctuations in intrathoracic pressure. During inspiration the right ventricle becomes more distensible as a result of the leftward shift of the septum and therefore can accommodate the increased venous return and filling volume without a change in diastolic pressure. In contrast, the distensibility of the left ventricle is reduced. However, because the left ventricle is now stiffer, the filling pressure of this chamber may remain invariant, despite a reduction in filling volume.

Preload and afterload: The magnitude and time course of wall force and stress vary throughout the cardiac cycle.[1] At end-diastole, the diastolic configu-

ration and pressure of either ventricle determine the distending force, or *preload,* on its wall. Preload determines muscle fiber length before contraction. Depolarized myocardium begins to contract, leading to the generation of pressure within the chamber. When chamber pressure exceeds that of the corresponding pulmonary or systemic circulation the ejection of blood commences. The force the myocardium must support during ejection, the *afterload,* is a function of the corresponding change in chamber configuration and pressure. Normally, afterload peaks shortly after the onset of ejection. However, because chamber size decreases more than pressure increases, afterload decreases during the remainder of ejection. Hence, the heart is normally able to partially unload itself during its contraction. Moreover, it should be apparent that a single value for force will not adequately describe afterload. The importance of the instantaneous variation in afterload is dramatized even further in the dilated and failing ventricle in which the reduction in chamber size during ejection is minimal. In this case the afterload trajectory becomes abnormal and, in fact, may increase rather than decrease during ejection.[1]

The Isovolumetrically Beating Ventricle

Cardiac muscle can generate force without muscle shortening (that is, an isometric contraction in which muscle length does not change). In the intact heart a contraction without the displacement of blood from the ventricle (for example; when the aortic valve is sewn together) is termed *isovolumetric.* The isovolumetrically beating heart can be used to describe the maximal force the myocardium can generate from a given volume. The greater the chamber volume, the larger the developed force, where force again is equal to the product of chamber pressure and the cross-sectional area of the chamber. This relation describes the Frank-Starling, or length-dependent, property of cardiac muscle. This slope of the maximal force-volume relation, which can be derived from a series of isovolumetric contractions of different filling volumes (Fig. 3), describes the contractile state of the myocardium. A nonparallel shift in the slope of this relation is created by an alteration in contractile state.[4,5] For example, a catecholamine will increase (Fig. 4) and propranolol will reduce this slope. Hence, for any given chamber volume the maximal force the myocardium is able to support is determined by the contractile state-dependent isovolumetric force-volume relation.

The Ejecting Ventricle

Pressure-volume relation: The contractile state-dependent isovolumetric force-volume relation also pertains to the ejecting ventricle in that this relation determines the limit to chamber volume displacement.[6] In Figure 4 the pressure-volume events for isovolumetric and ejecting contractions are shown for the right and left ventricles. In the ejecting ventricle, pressure is

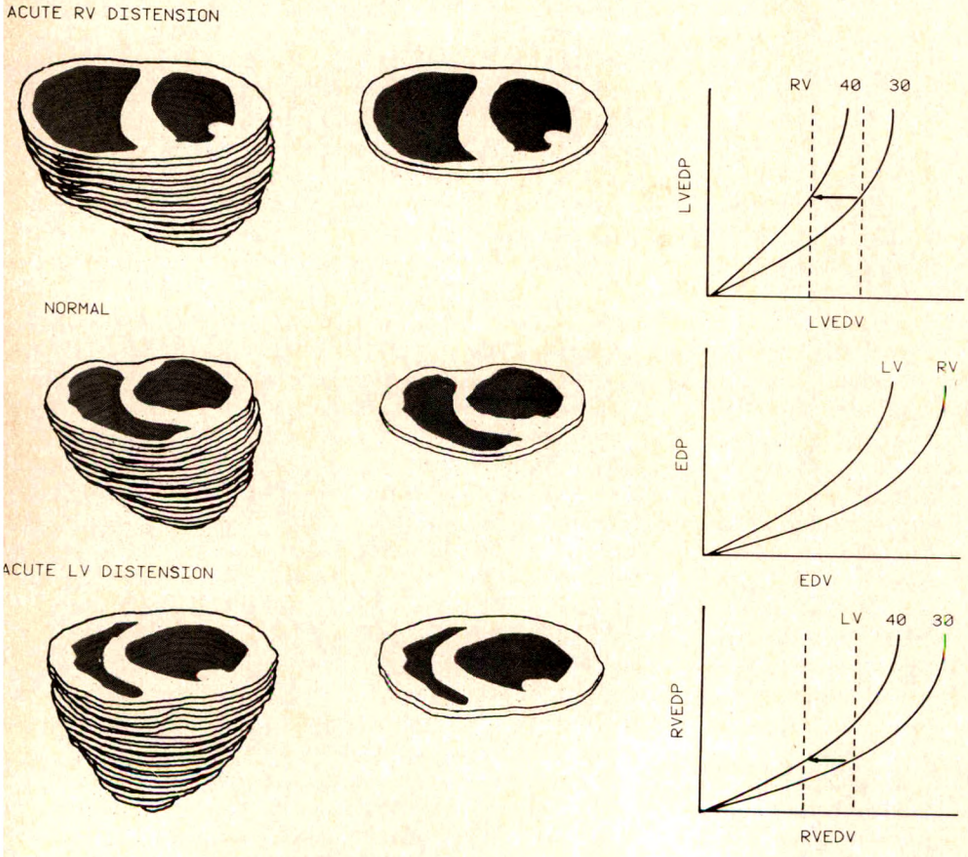

FIGURE 2. A computer reconstruction of the normal canine heart (**middle panel**) whose right and left ventricles were fixed at 6 and 12 cm H_2O, respectively. As depicted in the corresponding diastolic pressure-volume relation, the right ventricle (RV) is twice as distensible as the left ventricle (LV). With the acute distension of one ventricle, the interventricular septum is shifted toward the other ventricle. Because of this septal displacement the shape and distensibility of each ventricle are altered. For example, the greater the right ventricular volume (pressure-volume relation, **upper right**) the less distensible is the left ventricle. Because the left ventricle is now stiffer, its volume can decrease (**arrow**) without the occurrence of a change in filling pressure. EDP and EDV = end-diastolic pressure and volume, respectively; LVEDP and RVEDP = left and right ventricular end-diastolic pressure, respectively; LVEDV and RVEDV = left and right ventricular end-diastolic volume, respectively.

generated from end-diastole (point a) to the onset of ejection (point b) during the isovolumic phase of contraction; during ejection, ventricular volume decreases. When a systolic pressure is attained that is maximal for the given systolic chamber volume, ejection will cease (point c). This relation also pertains to the more accurate notation of load or wall force.[6] By increasing or decreasing contractile state, and thereby the slope of the maximal force-volume relation, the extent to which the ventricle is able to displace volume (that is, its stroke volume) for any afterload will correspondingly either increase (point c′ in Fig. 4) or decrease. Parallel shifts in the maximal force-volume relation occur independently of changes in contractile state. These shifts are the result of ventricular interaction.[7] For example, with right ventricular distension, the left ventricle is able to generate a greater force from any given volume (Fig. 5) because the interventricular septum has been shifted leftward, thereby minimizing the energy lost to septal movement.

Preload versus afterload: We have now established the limit of ventricular ejection and the importance of myocardial contractile state in determining this limit. Two other properties of cardiac muscle will determine the stroke volume from either ventricle. These include (1) the force that opposes fiber shortening, and (2) the length of cardiac muscle.[4,5,8] The greater the afterload opposing ejection the less the degree of shortening and chamber volume displacement (Fig. 6). This is true for both the right and left ventricles. Again recall that afterload is determined by both systolic pressure and chamber configuration during ejection. An excessive afterload may occur not only in aortic or pulmonary stenosis and systemic or pulmonary hypertension in which systolic pressure is increased, but also in the dilated failing ventricle (see earlier).

The filling volume and pressure of the ventricle are responsible for determining muscle length (preload) and the capacity of the ventricle to displace blood. Normally, for any given afterload, the larger the volume of the ventricle at the onset of ejection, the greater will be its stroke volume (Frank-Starling property of the heart). In the diseased heart the ventricle dilates in compensatory fashion to maintain pump function. However, a

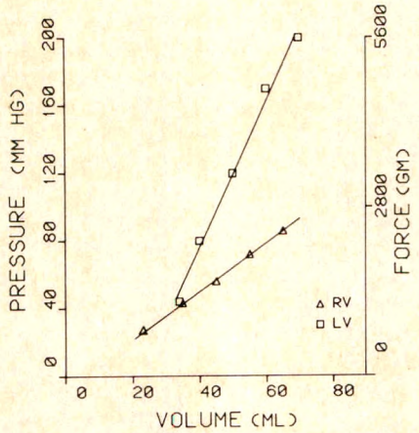

FIGURE 3. The pressure-volume and force-volume relations for the isovolumetrically beating right (RV) and left (LV) ventricles. Force was calculated from the product of ventricular pressure and the cross-sectional area of the left and right ventricular chambers.

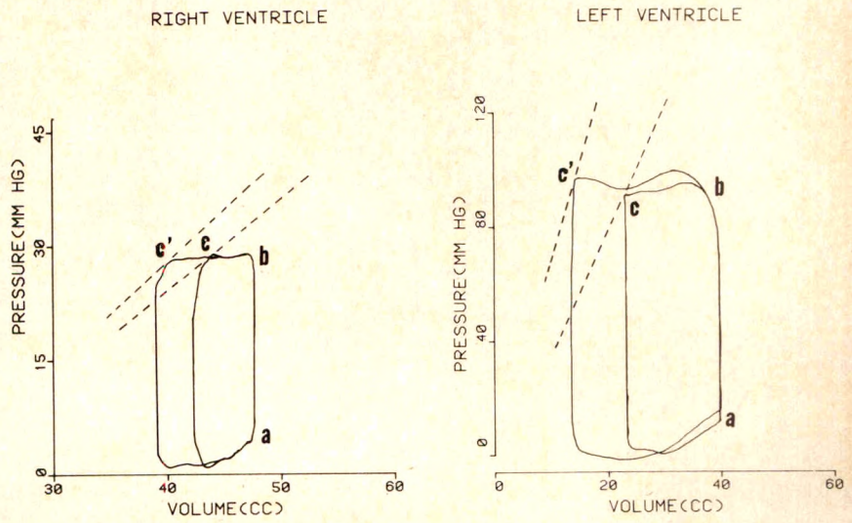

FIGURE 4. The interrelation between the isovolumetric pressure-volume relation and an ejecting contraction. Shown are end-diastolic (a), onset (b) and end-ejection (c) values before and after the increment in myocardial contractile state (dobutamine, 6 μg/min). End-ejection pressure and the extent of ejection (that is, stroke volume) are related to the isovolumetric maximal pressure-volume relations. An increase in stroke volume occurs with dobutamine because the ventricle can now eject to a greater extent (to point c′).

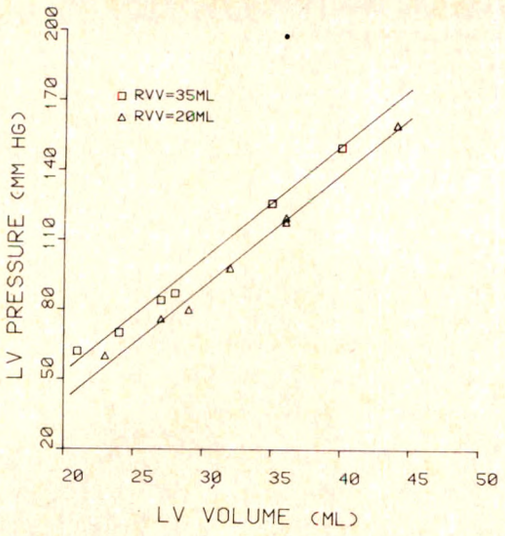

FIGURE 5. A parallel shift in the isovolumetric pressure-volume relation of the left ventricle (LV) occurs when the volume of the right ventricle (RVV) increases from 20 to 35 ml.

ventricle twice normal size may have a stroke volume that only approximates the output of the normal heart because the contractile state is concomitantly reduced.

The contractile mechanics of the myocardium describe the pumping behavior of the right and left ventricles. Up to this point, the importance of preload, afterload and myocardial contractile state have been emphasized in regulating the performance of the muscular pump. The mechanical interaction between ventricles created by the interventricular septum, pericardium and variations in pleural pressure also determine the size, shape and load of the ventricles. These factors are particularly important when one is considering cardiac performance in the patient who has respiratory failure.

Interaction of the Right and Left Ventricles

As noted earlier, the myocardium is composed of muscle fibers tethered within a supportive network of collagen. Recent observations from this laboratory[8a] indicate that the muscle fiber alignment of the interventricular septum resembles that of the left ventricular free wall. Hence, on morphologic grounds the septum can be considered part of the left ventricle. However, because the right and left ventricles are aligned in series and mechanically coupled, a perturbation in the mechanical events of one ventricle will influence the behavior of the other ventricle, and in nonsteady state conditions the output of the two ventricles may not be balanced. Eventually, however, a steady state of balanced outputs must occur if pulmonary or systemic venous congestion is to be avoided.

To discern the relative contribution of the septum, pericardium and pleural pressure to the mechanical interaction of the ventricles, it is necessary either to segregate each component while maintaining the heart intact or to monitor carefully the physiologic behavior of each component with the chest intact. We have chosen the former approach using an isolated canine heart.

The Direct Interaction Between Ventricles

Diastolic interplay between ventricles: With our isolated heart preparation the volume in each ventricle can be controlled.[9] Hence, it is possible to assess the pressure-volume relation of one ventricle while the filling volume in the other ventricle is varied. Figure 7 shows a typical response, with and without the pericardium. It can be seen that for any constant volume of the right ventricle (15, 34 or 39 cc, upper right panel), this chamber's filling pressure increased nonlinearly as the volume of the left ventricle was progressively increased over the filling pressure range of 0 to 20 mm Hg. The diastolic interplay between ventricles was more pronounced the greater the volume of the right ventricle. A similar response in left ventricular diastolic pressure was observed as right ventricular volume was increased over the same range in filling pressure (lower right panel, Fig. 7). The change in diastolic pressure that occurred in each ventricle was quite similar in 15 hearts examined and ranged from 1 to 3.5 mm Hg in the right ventricle and 0.7 to 4.9 in the left ventricle.[7]

Systolic interplay between ventricles: During systole the pressure in one ventricle will also influence the systolic pressure developed in the other. The systolic

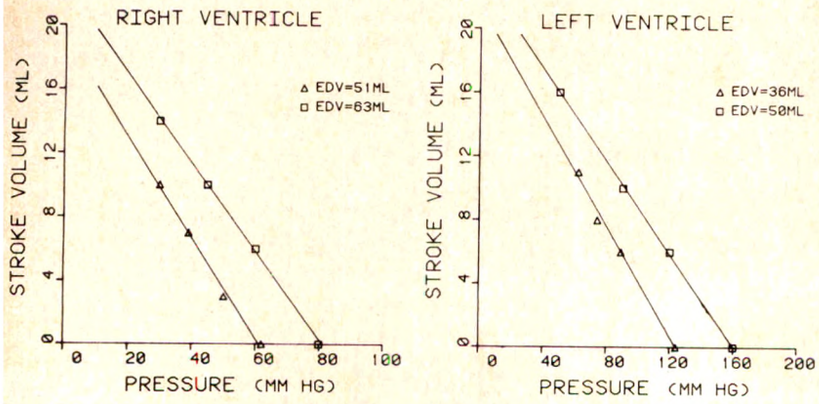

FIGURE 6. An inverse relation exists between stroke volume and ejection pressure in either ventricle. The greater the end-diastolic volume (EDV) of the ventricle the greater its stroke volume for any given ejection pressure.

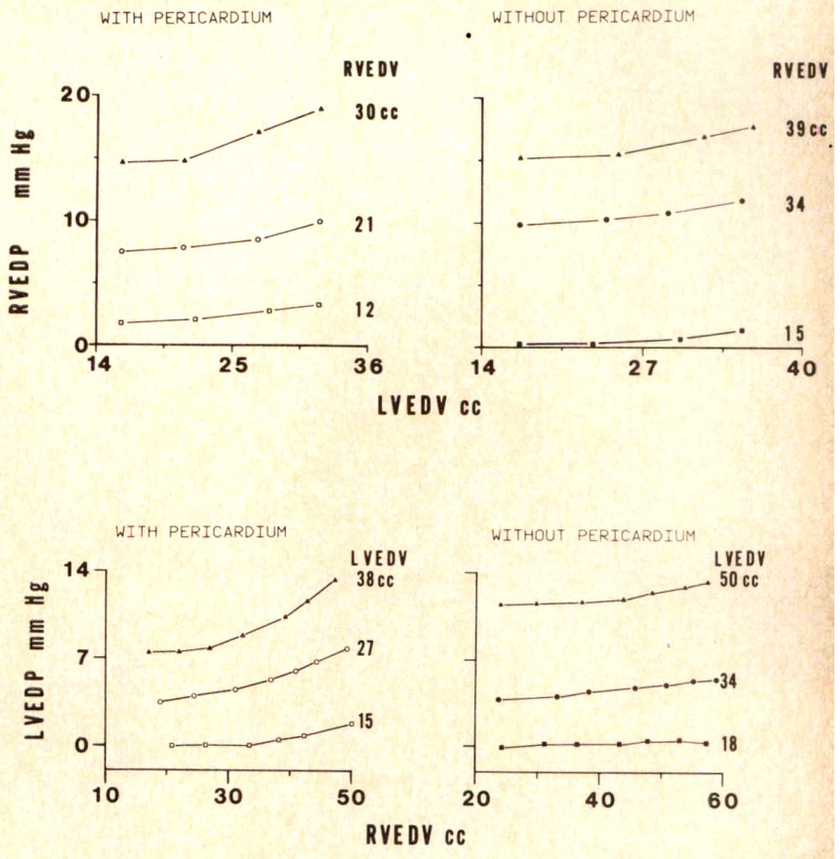

FIGURE 7. The diastolic interaction between ventricles in the absence of the pericardium is demonstrated in the **right panels.** The pericardium serves to accentuate this interaction (**left panels**). LVEDP and RVEDP = left and right ventricular end-diastolic pressure, respectively; LVEDV and RVEDV = left and right ventricular end-diastolic volume, respectively. Modified from Janicki and Weber[7] with permission of the *American Journal of Physiology*.

interplay between ventricles particularly applies to the influence that the left ventricle exerts on right ventricular pressure development. For example, Figure 8 shows that the systolic pressure of the isovolumetrically beating right ventricle became greater as left ventricular systolic pressure increased. The slope of each relation was quite similar, indicating that for any volume, the right ventricle was equally sensitive to left ventricular systolic pressure. The influence of right ventricular systolic pressure on left ventricular pressure is only apparent when the pressure generated by the left ventricle is markedly reduced to hypotensive levels and comparable with right ventricular systolic pressure. Hence, this interplay is minimal under normal physiologic conditions.

Interventricular septum: As several investigators[10–15] have previously demonstrated, the interaction between ventricles during diastole and systole reflects the importance of the interventricular septum and its position. When the transseptal force gradient favors a rightward shift of the septum, as in acute left ventricular distension (Fig. 2), diastolic pressure in the right ventricle either increases or remains invariant despite a reduction in chamber volume. The reverse is also true for the left ventricle. The septal surface forces also serve to buttress the septum during systole and retard its motion so that the pressure developed by either ventricle becomes greater. The influence of right ventricular volume on the maximal pressure-volume relation of the isovolumetrically beating left ventricle is depicted in Figure 5. As right heart volume is increased, a parallel leftward shift of the left ventricular pressure-volume relation occurs. The relative importance of septal motion to ventricular interaction and pump function was also evident in the classic experiments of Starr,[14] who found that central venous pressure and cardiac output remained normal after massive destruction of the canine right ventricular free wall. In contrast, right heart performance deteriorates when right ventricular infarction occurs in the presence of an infarcted septum.[15,16]

The Pericardium and Ventricular Interaction

The pericardium surrounds the atria and ventricles, and its viscoelastic properties impose a physical constraint on acute cardiac distension.[7] As one would expect from its curvilinear pressure-volume relation, the pericardium exerts its predominant influence at larger cardiac volumes. After pericardiectomy the greatest reduction in filling pressure in either ventricle occurs at larger filling volumes. Over the range of filling pressures examined (0 to 20 mm Hg) the average upward shift in end-diastolic pressure of the right and left ventricles due to the pericardium was identical (mean ± standard error of the mean +4.3 ± 0.6 and +4.6 ± 1.0 mm Hg, respectively).

Because filling pressure is reduced in either ventricle after pericardiectomy, although ventricular volume is held constant, the distending force (pressure and di-

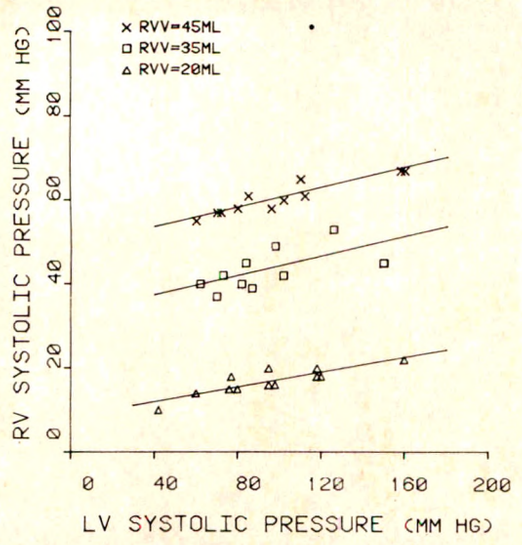

FIGURE 8. Left ventricular systolic pressure development contributes to the pressure generated by the right ventricle (RV). The extent of this interaction appears to be equivalent for several right ventricular diastolic volumes (RVV).

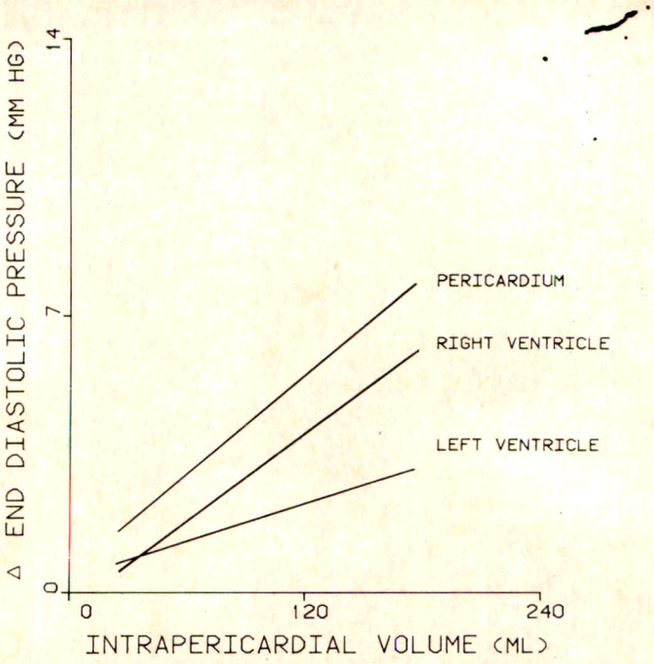

FIGURE 9. The changes (Δ) in end-diastolic pressure for the pericardium (PEDP) and right (RVEDP) and left (LVEDP) ventricles are shown as a function of intrapericardial volume. As pericardial volume increases the external pressure on the ventricles also increases, augmenting their diastolic pressure and reducing the effective compliance of the chambers. Modified with permission.

mension), or preload, on the myocardium is also reduced. Commensurately, the developed systolic pressure will decrease after removal of the pericardium. This effect was also similar in both the right and left ventricles (−5.8 ± 2.2 and −4.1 ± 2.0 mm Hg, respectively).

By imposing a physical constraint on the expansion of either ventricle, the pericardium enhances the degree of ventricular interaction (left panels, Fig. 7). These responses can be compared with those that occur when the pericardium is absent (right panels, Fig. 7). In the presence of the pericardium the change in diastolic pressure caused by ventricular interaction (filling pressure range 0 to 20 mm Hg) ranged from 1.3 to 5.6 mm Hg in the right and from 1.4 to 11.0 mm Hg in the left ventricle. However, the degree of systolic interaction after pericardiectomy was more variable. Normally the mechanical influence of the pericardium during systole is minimal as cardiac volume declines.

Transmural Pressure

The heart is surrounded by the pericardium and situated in the thorax. The pressures inside the pericardial sac and intrathoracic cavity determine the pressure exerted on, or external to, the heart. Intrapericardial and intrathoracic pressures are normally quite similar and range from −3 mm Hg at end-expiration to −6 mm Hg with inspiration.[17] The degree of negative intrathoracic pressure can be increased dramatically with the augmented inspiratory effort associated with acute bronchospasm (resistive loading) or a Müller maneuver (that is, forced inspiration against a closed glottis). On the other hand, a Valsalva maneuver, pneumothorax, mechanical ventilator or conditions of positive expiratory pressure serve to create a positive intrathoracic pressure.

In considering the influence of pleural pressure on the heart, and specifically its ventricles, it is best to speak in terms of the transmural pressure (that is, the difference in pressure across the myocardium or between the inside and outside of the ventricle).[18] For either ventricle, transmural pressure describes its effective filling pressure; the transmural pressure of the pulmonary artery or aorta indicates the pressure that opposes ventricular ejection. Because ventricular volume is subject to change, transmural ventricular diastolic pressure is increased with negative intrathoracic pressure and decreased when the pressure within the pleural space becomes positive. In addition to the influence of transmural pressure on ventricular filling, the venous return to the right heart chambers is dependent on the gradient in pressure between the extra- and intrathoracic veins. Positive intrathoracic pressure reduces this gradient, whereas negative pressure raises the gradient favoring venous return. For example, if this gradient were 5 mm Hg, a 5 mm Hg reduction in pleural pressure would increase this gradient to 10 mm Hg.

Reducing transmural pressure: To isolate the influence of a positive external pressure (that is, reduced transmural pressure) on the behavior of the ventricles and their interaction without the influence of alterations in lung volume, we monitored the responses of right and left ventricular pressure to increasing levels of intrapericardial pressure in the open chest dog in which ventricular volumes were free to change (Fig. 9).[18a]

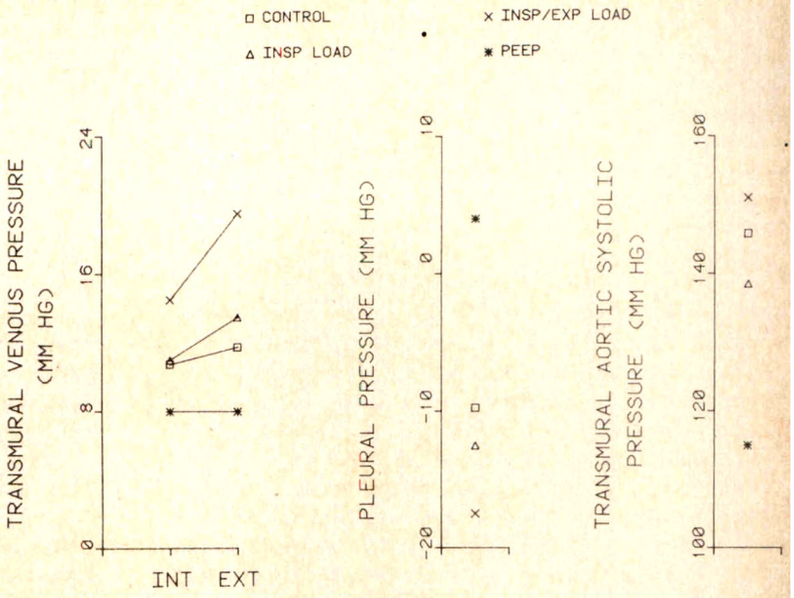

FIGURE 10. Intra- (INT) and extrathoracic (EXT) venous pressures were measured and referenced to pleural pressure, the difference being transmural venous pressure. The alteration in transmural venous and aortic pressures that occur during negative and positive variations in pleural pressure are presented for the following conditions: (1) control (spontaneous respirations in an intubated, anesthetized dog breathing through a Hans-Rudolph valve); (2) inspiratory (INSP) load (a narrowing [2 mm orifice] of the inspiratory port of the valve); (3) inspiratory/expiratory (INSP/EXP) load (2 mm orifice at the endotracheal tube); and (4) positive end-expiratory pressure (PEEP) (15 cm H_2O positive end-expiratory pressure during assisted ventilation). The difference between extra- and intramural venous pressure equals the venous filling gradient to the right heart chambers.

The average increase in pericardial and ventricular end-diastolic pressures are given as a function of pericardial volume in Figure 9. These responses in pericardial and ventricular pressure to a pericardial effusion were calculated by subtracting the initial level of pressure in the pericardium and the right and left ventricles from the corresponding pressures observed during tamponade. The amount by which each pressure increased during tamponade differed; the increase in pressure in the pericardium was greatest, whereas that in the left ventricle was least. In fact, when left ventricular end-diastolic pressure was 12 mm Hg or more at the onset of the infusion, left ventricular pressure actually decreased as pericardial volume increased. Thus, the increase in filling pressure in the right ventricle was greater than that in the left ventricle and, in all likelihood, represents the difference in distensibility between ventricles; that is, the stiffer left ventricle will have a larger decrease in diastolic pressure for any given reduction in its volume. Accordingly, with increments in external pressure its filling pressure changes less, or may even decrease, in comparison with the response in pressure in the more distensible right ventricle. Hence, even though a diastolic pressure in the two ventricles may be 15 mm Hg with a chronic pericardial effusion the difference in ventricular distensibility may account for the greater decrement in filling pressure in the right as compared with the left ventricle after pericardiocentesis.[19]

Because the effective ventricular filling pressure is the transmural diastolic pressure of the ventricle, it is clear from Figure 9 that during tamponade the transmural pressure for both ventricles was decreasing as pericardial pressure increased. However, because the increase in end-diastolic pressure in the left ventricle was less than that in the right ventricle the transmural pressure declined by a lesser amount in the right ventricle. Thus, the ability of either ventricle to maintain its effective filling pressure during tamponade depends on the increase in filling pressure with respect to the increase in pericardial pressure. Similarly, the preservation of the filling pressure gradient to the right atrium during tamponade or any increase in extracardiac pressure, such as positive expiratory pressure (Fig. 10), is dependent on a compensatory increase in peripheral venous tone to maintain venous return.

Transmural pressure is also reduced when intrathoracic pressure is increased during the strain phase of a Valsalva maneuver or with mechanical ventilation. The extent to which intrathoracic pressure increases is dependent on the compliance of the chest wall and lungs, lung volume, time in which the lungs are held in the inflated state and the extent to which airway pressures are transmitted to the intrathoracic vessels. During the strain phase of a Valsalva maneuver, Brooker[20] and Buda[21] and their co-workers found that both end-diastolic and end-systolic volumes as well as cardiac output decreased, as one would expect with a reduction in transmural ventricular pressure and a decrease in the venous gradient. However, transmural pressure in the intrathoracic aorta would decrease during the Valsalva maneuver.[20,21] On the basis of our knowledge of the behavior of the muscle pump, this reduction in transmural aortic pressure would favor an increase in stroke volume. This effect is obviously offset by the greater decrease in ventricular transmural pressure and the end result is a decrease in stroke volume.

Intermittent and continuous positive pressure ventilation are used to increase arterial partial pressure of oxygen in patients with acute respiratory failure. Although arterial partial pressure of oxygen may be increased with assisted ventilation, cardiac output often decreases as pleural pressure is increased, com-

promising oxygen delivery. The mechanisms that account for the decrease in cardiac output are not fully understood. However, the following physiologic consequences of positive pleural pressure are certainly operative. Transmural ventricular pressure and the venous gradient across the thorax decrease during positive pressure ventilation (Fig. 10). As a result, venous return and right ventricular diastolic volume and output are attenuated.[22] If the effective distensibility of the right ventricular chamber were also reduced by positive intrathoracic pressure (analogous to a pericardial effusion) this would further contribute to a reduction in the filling volume of this chamber, even though filling pressure may not decrease.[23,24] The same would also apply to left ventricular distensibility,[25] which also would tend to minimize the change in filling pressure. Although transmural pulmonary arterial pressure should be less, the positive pleural pressure contributes a compressive force to the pulmonary vasculature and may serve to elevate pulmonary vascular resistance depending on the functional residual capacity. The impedance characteristics of the pulmonary circulation would also be distorted by the mechanical ventilation and the duration of each inflation. The fact that transmural pulmonary arterial pressure actually increases in the presence of diminished right heart output[26] lends support to this interpretation and may also contribute to the preservation or elevation in filling pressure, and perhaps even increase right ventricular diastolic volume.[24] Hence, there are a variety of purely mechanical explanations favoring reduction in cardiac output on the basis of reduction in right ventricular output and diminished left ventricular filling.

In contrast, other investigations[23,24,26] have considered this decrease in cardiac output the result of indirect mechanisms, including a depression in myocardial blood flow, circulating vasoactive substances released from the lung, reflex cardiovascular depression accompanying lung inflation, and the activation of neural receptors within the lung. The actual mechanism that accounts for the decrease in cardiac output with positive pressure ventilation, whether mechanical or indirect, requires further investigation.

Increasing transmural pressure: Intrathoracic pressure can be reduced substantially during a Müller maneuver (that is, an inspiratory load) or with the forced inspiratory and expiratory effort associated with marked airway resistance (that is, acute bronchospasm or chronic obstructive airway disease). As a result, the transmural ventricular filling pressure and the venous gradient to filling both increase, favoring an enhanced venous return (Fig. 10) and an increase in right ventricular volume. However, the increase in venous return is not proportional to the decrease in pleural pressure because the extrathoracic veins are collapsible. The greater the central venous pressure (as in cor pulmonale, biventricular failure or pericardial effusion) the greater the venous return for any given decrease in intrathoracic pressure.

The increase in right ventricular filling volume and pressure alters the transseptal force gradient, promoting a flattening and leftward shift of the septum that reduces the size of the left ventricular chamber and alters its shape (Fig. 2). As a consequence, the effective compliance of the left ventricular chamber is reduced as is its filling volume. Together the reduction in filling volume and elevation of aortic transmural pressure[27,28] account for the decrease in left ventricular stroke volume and the resultant decrease (less than 10 mm Hg) in arterial pressure that normally accompanies inspiration. More marked reductions in pleural pressure accentuate this disequilibrium and account for the "paradoxical" pulse observed in the patient with acute asthma.

With cardiac dilatation the pericardium will accentuate the increase in right ventricular filling pressure and the encroachment of the septum within the left ventricle when intrathoracic pressure becomes more negative. Changes in left ventricular geometry and distensibility may also account for the relative impairment in left ventricular pump function noted in patients with chronic airway disease.[29] Similarly, the association of mitral valve prolapse with atrial septal defect may be the result of altered left ventricular geometry and the leftward position of the interventricular septum with chronic right heart distension.[30]

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Control of Cardiac Output by Systemic Vessels

Circulatory Adjustments to Acute and Chronic Respiratory Failure And the Effect of Therapeutic Interventions

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The circulation requires the heart to pump blood from the venous to the arterial bed. The factors that determine venous flow into the heart are mean pressure in the systemic vasculature, right atrial pressure and the resistance to venous return. The mean pressure in the systemic vasculature is a function of the stressed vascular volume and the systemic vascular compliance. Right atrial pressure depends on many factors. These include the contractile state of the right and left ventricles, the load on the right and left ventricles, the presence or absence of pericardial effusion, and alterations in pleural pressure that might occur with positive pressure ventilation. The resistance to venous return tends to stay remarkably constant, but can be reduced by significant arteriovenous shunting.

The right ventricle has a relatively high diastolic compliance. Because of this, changes in volume of the right ventricle are associated with only modest increases in right atrial pressure. Therefore, as load on the right ventricle increases, mean systemic vascular pressure needs to increase only a small amount to maintain cardiac output. If right atrial pressure increases sufficiently as a result of a greatly increased load on the right ventricle, as in pulmonary embolism, hypoxic pulmonary vasoconstriction or chronic respiratory failure, the increase in mean systemic vascular pressure necessary to maintain normal venous return, and therefore cardiac output, may lead to signs of right heart failure, with no change in the slope of the right heart function curves. The implications of this phenomenon are important in managing patients with acute and chronic respiratory failure. Positive pressure ventilation, diuretic agents, cardiac glycosides and other inotropic or vasoactive drugs will influence the relation between the mean systemic pressure and right atrial pressure. Therefore, these treatment modalities may unexpectedly alter cardiac output if the systemic vascular effects are not kept in mind.

This review presents an integrated approach to circulatory function based on the factors that influence venous return. The circulatory adjustments to acute and chronic respiratory failure and the effect of various therapeutic interventions on venous return are discussed as well. With an understanding of the systemic vascular mechanics that influence venous return, and therefore cardiac output, circulatory derangement in patients treated for respiratory failure can be better managed.

Cardiac output depends on a functioning heart and on the amount of blood presented to the heart to be pumped out. Thus, the heart can be conceptualized as a pump in a closed loop circuit of elastic tubes (Fig. 1). The central compartment is portrayed in a single box. For the purposes of this review, this compartment is of interest because the downstream pressure for the entire circulation can be thought of as the right atrial pressure. Even from this schematic representation, it is obvious that right atrial pressure is contingent upon the interdependent relation of the right heart chambers with the lungs, the left heart chambers and the surrounding pressures of all these structures.

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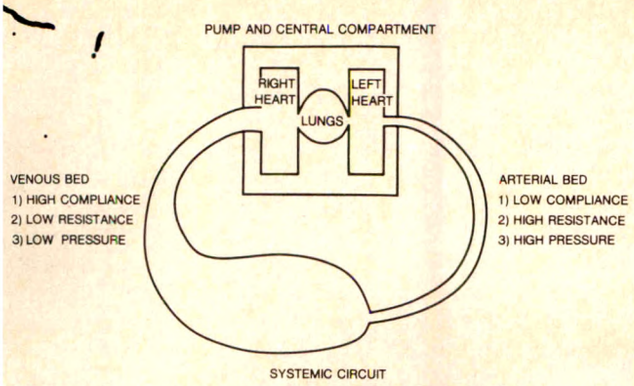

FIGURE 1. Schematic diagram of the circulatory system.

The systemic circuit in Figure 1 consists of an arterial side and a venous side in series. The arterial portion of the circuit has a low compliance and a high resistance to flow; the venous side has a high compliance and a low resistance to flow. In the dog, arterial compliance is about 1/20 that of venous compliance, and arterial resistance is about 20 times venous resistance.[1] Under ordinary flow conditions, arterial pressure is about 10 times greater than venous pressure. However, if the circulation were stopped and allowed to come to equilibrium, the pressure everywhere in the circulatory system at any given hydrostatic level would be the same. This pressure has been termed mean systemic pressure by Weber, as cited by Starling.[2]

Mean Systemic Pressure

Mean systemic pressure is determined by vascular compliance and the stressed volume in the vascular bed.

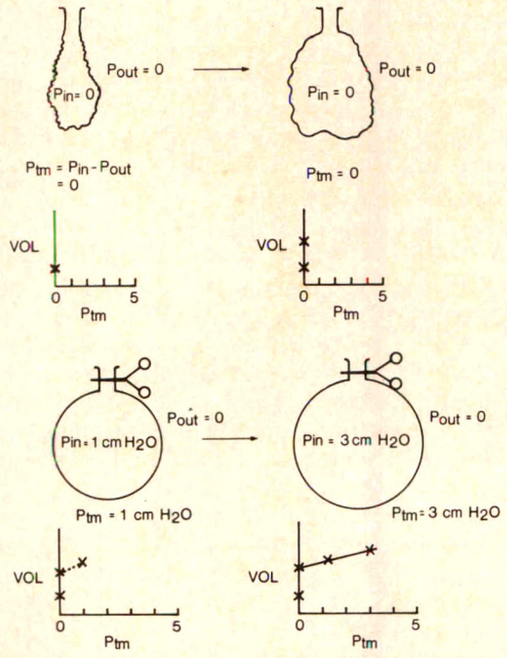

FIGURE 2. An example demonstrating the concept of unstressed volume. P_{in} = pressure inside the large floppy balloon; P_{out} = pressure outside the large floppy balloon; P_{tm} = transmural pressure; VOL = volume within the balloon.

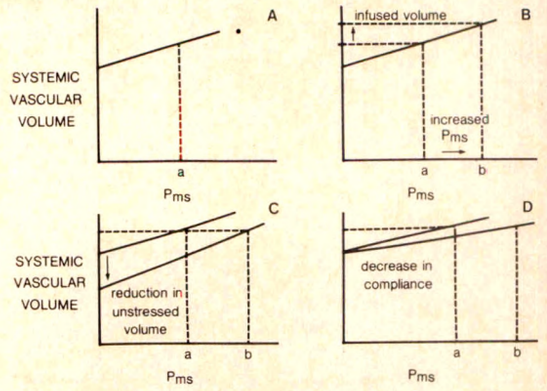

FIGURE 3. Mean systemic pressure (P_{ms}) can be increased by the addition of stressed volume to the systemic vascular circuit (**A**). This can occur in three ways. **B,** one way is an infusion of volume into the systemic vasculature. **C,** another way is a reduction in the unstressed volume of the vasculature at constant intravascular volume, which could occur with vasomotor reflexes. **D,** another method for increasing P_{ms} at a constant vascular volume is by a decrease in systemic vascular compliance.

Stressed volume is the volume associated with a positive change in transmural pressure. Unstressed volume is the volume in an elastic container that is *not* associated with a positive transmural pressure. Consider a large, floppy bag open to atmosphere (Fig. 2). The pressures inside and outside the bag are atmospheric. If some volume is added to the bag but the top is kept open to atmosphere, the pressure inside the bag is still zero and the transmural pressure is still zero. As more volume is added to the bag, there will be a point at which the top must be sealed because the pressure inside the bag will be greater than atmospheric pressure. This is the unstressed volume. The transmural pressure increases with the addition of more volume to the sealed bag. The slope of a line connecting the pressure volume points is the compliance of the bag. Changing the axes to represent mean systemic pressure on the abscissa and systemic vascular volume on the ordinate (Fig. 3) demonstrates that mean systemic pressure is a simple function of vascular stressed volume and vascular compliance.

Vascular Pressure and Volume Distribution With Flow

With the circulation completely stopped and the pressure equilibrated, if the heart begins to beat, blood is pumped from the venous side of the circulation into the arterial side. Because the arterial bed has a relatively high resistance to flow, not all of the blood added to the arterial side drains out before the next beat. As each succeeding beat increases the volume in the arterial bed, pressure will continue to increase until it is high enough to allow all the stroke volume to drain across the arterial resistance into the venous bed. The pressure in the arterial bed increases with the added volume as a function of its compliance. Because arterial compliance is low, a small amount of blood added to the arterial side causes a relatively large increase in arterial pressure. In this circuit (Fig. 1), the blood added to the arterial side comes at the expense of the volume in the venous bed.

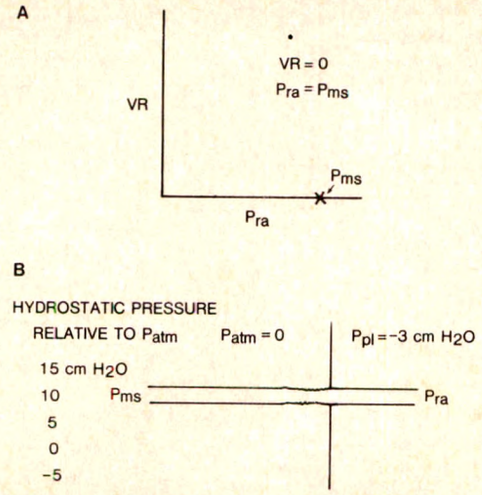

FIGURE 4. A, when there is no flow in the circulatory system, there is no venous return (VR), and pressure in the right atrium (P_{ra}) is equal to the mean systemic pressure (P_{ms}). **B,** a model of the circulation with no flow. The scale on the **left** shows that mean systemic pressure and right atrial pressure are both equal to 10 cm H_2O relative to atmospheric pressure (P_{atm}). Therefore, there is no flow. Note that the transmural right atrial pressure would be 13 cm H_2O.

Because the compliance of this bed is very high, a shift of volume out is associated with only a small change in venous pressure.

When the heart starts to beat, it increases the pressure on its outflow side by adding volume to the systemic circuit from the central compartment. As the left heart chambers are refilled from the right heart chambers, the volume and, concurrently, the pressure are reduced in the right side of the heart. With a reduced pressure in the right atrium, the inflow side of the heart, blood flows from the circuit to the pump.

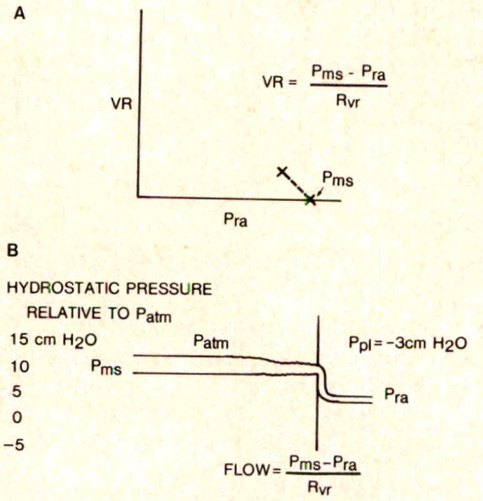

FIGURE 5. A, when right atrial pressure (P_{ra}) is reduced at a given mean systemic pressure (P_{ms}), venous return (VR) is determined by the difference between mean systemic and right atrial pressure divided by the resistance to venous return (R_{vr}), which is the reciprocal of the slope of the line. **B,** a model of the circulation with flow and right atrial pressure greater than atmospheric pressure (P_{atm}). The scale on the **left** shows that mean systemic pressure is unchanged and is still 10 cm H_2O. Right atrial pressure is now 5 cm H_2O. The pressure gradient for flow is mean systemic pressure minus right atrial pressure; this is 5 cm H_2O. Note that transmural right atrial pressure is 8 cm H_2O.

For the purposes of this discussion, we will assume that outflow and inflow are equal, a reasonable assumption in a steady state. With this condition, it is obvious that vascular stressed volume has not changed, although the pressures around the circuit have changed; arterial pressure is increased a great deal, and venous pressure is reduced a small amount. Because the stressed volume in the circuit has not changed but is merely redistributed, to calculate mean systemic pressure during flow one would have to know the pressure in each segment of the circuit and weigh that pressure as a function of compliance of the segment, as a fraction of total systemic compliance. If total systemic compliance is unchanged, then mean systemic pressure during flow is the same as when there is no flow.

Determinants of Venous Return

Right Atrial Pressure

The amount of venous return and, therefore of steady state cardiac output, is proportional to the difference between mean systemic pressure and right atrial pressure. However, for any mean systemic pressure there is a limit to how much venous return can occur as right atrial pressure is reduced. If the latter is sufficiently reduced, the inflow veins will undergo a decrease in pressure. If this pressure becomes less than the surrounding pressure, the veins will collapse.[3,4] This is analogous to the situation in the lung where inflow pressure or pulmonary arterial pressure is greater than alveolar pressure, but alveolar pressure is greater than outflow pressure or pulmonary venous pressure. This is the zone II described by West et al.[5] The driving pressure for flow is pulmonary arterial pressure minus alveolar pressure; reducing pulmonary venous pressure does not influence flow. Indeed, the vessels exposed to alveolar pressure in zone II behave like Starling resistors, which limit flow as downstream pressure is reduced.[5] In this analogy, mean systemic pressure is equivalent to pulmonary arterial pressure, right atrial pressure is equivalent to pulmonary venous pressure, and atmospheric pressure is equivalent to alveolar pressure. Therefore, lowering right atrial pressure below the surrounding pressure of the collapsible veins will not influence venous return. Graphically, these concepts are represented in Figures 4 to 6. At zero venous return (Fig. 4A), that is, at no flow in the system, the pressure everywhere in the system is the same and equal to mean systemic pressure. Therefore, right atrial pressure at zero flow is equal to mean systemic pressure. This condition is shown in a model in Figure 4B.

If right atrial pressure is lowered by starting the pump (Fig. 5A), mean systemic pressure does not change, but a pressure gradient for venous return is created. The amount of venous return is proportional to the difference between mean systemic and right atrial pressures and is inversely related to the resistance to venous return. The slope of the line connecting the two points is the reciprocal of this resistance. Figure 5B shows the

relation in terms of our model: Right atrial pressure is lower than mean systemic pressure but is greater than atmospheric pressure, the pressure surrounding the collapsible veins. As right atrial pressure is further lowered with the volume in the circuit unchanged, venous return continues to increase (Fig. 6A). As right atrial pressure falls below the pressure surrounding the veins entering the thoracic cavity, they tend to collapse and limit venous return. In Figure 6B, right atrial pressure is lower than the pressure surrounding the collapsible veins, causing them to collapse and limit flow. To complete the zone II of the analogy of West et al.,[6] right atrial pressure is equivalent to pulmonary venous pressure, atmospheric pressure is equivalent to alveolar pressure and mean systemic pressure is equivalent to pulmonary arterial pressure.

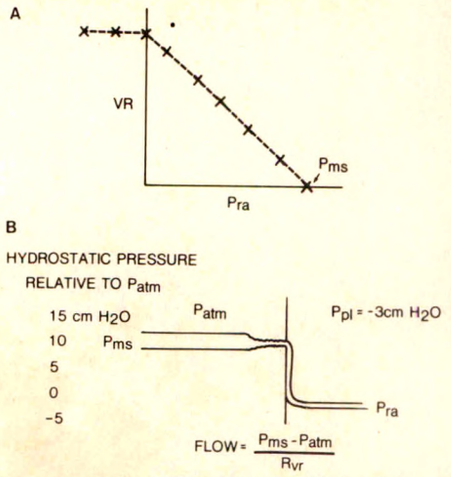

FIGURE 6. A, as pressure in the right atrium (P_{ra}) is reduced more and more at a given mean systemic pressure (P_{ms}), venous return (VR) continues to increase until right atrial pressure decreases below a certain value. Once right atrial pressure reaches a low enough value, the pressure in the veins entering the thorax falls below the pressure surrounding them, and they collapse. The surrounding pressure of the veins is then the pertinent back pressure in determining flow. **B,** a model of the circulation with right atrial pressure below the pressure surrounding the collapsible veins. In this example that pressure is atmospheric (P_{atm}). The scale on the **left** shows that mean systemic pressure is still 10 cm H_2O. Right atrial pressure is −2 cm H_2O. Therefore, the pressure gradient for flow is mean systemic pressure minus atmospheric pressure. This is 10 cm H_2O. A further decrease in right atrial pressure will not influence the flow. Note that transmural right atrial pressure is 1 cm H_2O.

Resistance to Venous Return

Further lowering of right atrial pressure does not increase venous return. However, venous return can be increased if mean systemic pressure is increased (Fig. 7B) or if the resistance to venous return is decreased (Fig. 7A). The resistance to venous return is an average of all the regional resistances from the systemic circuit back to the right atrium. Each regional resistance is weighted by its contribution to the entire systemic vascular compliance and the fraction of the cardiac output draining from each region.[1] As a practical matter, it is known that the resistance to venous return remains remarkably constant under a wide variety of circumstances, increasing only slightly with large adrenergic stimulation.[1,6] A clinically important effect of a reduced resistance to venous return is arteriovenous shunting. This reduces the resistance to venous return and allows an increase in cardiac output with no change in mean systemic or right atrial pressure[7] (Fig. 7A). Hypoxia, exercise or even redistribution of cardiac output by nonuniform changes in arterial resistance can also alter the resistance to venous return. Because alterations in resistance to venous return in respiratory failure have not been studied to any great extent, changes in mean systemic pressure currently have greater clinical importance.

Mean Systemic Pressure

Maintaining adequate cardiac output is particularly important in patients with increased pressures in the right side of the heart. Increased pressure may be a result of left heart failure, chronic obstructive pulmonary disease, pulmonary emboli or hypoxic vasoconstriction. Positive pressure ventilation, especially with added positive end-expiratory pressure, also will cause right atrial pressure to increase in relation to atmospheric pressure even though transmural right atrial pressure may have decreased. Clearly, if right atrial pressure increases in relation to atmospheric pressure, mean systemic pressure must increase just as much if normal venous return, and therefore cardiac output, is to be maintained.

Mean systemic pressure can be changed by adding volume to the circuit (Fig. 3A). This can come by infusion, but anything that increases the stressed volume of the circuit will have the same effect. Figure 3B shows that infusion of volume increases mean systemic pressure as a function of vascular bed compliance. However, with no change in vascular volume, mean systemic pressure can be increased by decreasing the unstressed volume (Fig. 3C). This can result from contraction of the muscles in the walls of the vascular bed, as occurs reflexly when there is blood loss. With no change in vascular volume, decreasing the vascular compliance itself will result in an increase in mean systemic pressure, as well (Fig. 3D).

Another way mean systemic pressure can be increased is by translocation of blood from the central compartment to the systemic circuit.[8] The net effect

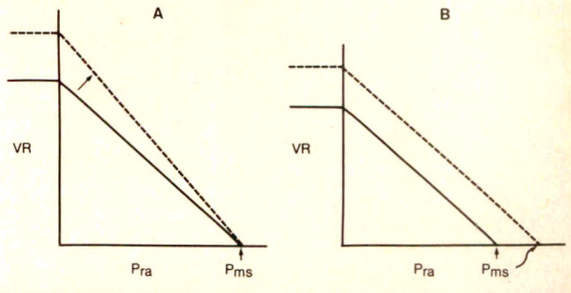

FIGURE 7. Two ways venous return (VR) can be increased are depicted. **A,** one way is for resistance to venous return to decrease. **B,** another way is for mean systemic pressure (P_{ms}) to be increased with resistance to venous return unchanged. P_{ra} = right atrial pressure.

of this is to decrease right atrial pressure and, by adding stressed volume to the systemic circuit, to increase mean systemic pressure. This can occur if the heart has either an improvement in inotropic state at a constant afterload or a reduction in afterload. Therefore, under conditions of acute or chronic increases in right heart pressure, the body has several mechanisms available to increase venous return. And, in a steady state, no matter how excellent cardiac function, the heart can pump out only what is returned.

The Cardiac Function Curve

For a given stressed vascular volume and systemic vascular compliance, mean systemic pressure is set, and the resistance to venous return can be considered relatively constant. Therefore, in the absence of pulmonary hypertension or right heart dysfunction, left ventricular function will ultimately determine right atrial pressure and therefore venous return. Of course, this is limited by the Starling resistor effect, described earlier.

In Figure 8A a venous return curve is plotted with a simultaneous cardiac function curve. It can be seen that cardiac output is uniquely determined by the intersection of the two curves. It should be remembered that the cardiac function curve relates cardiac output to all of the factors in the central compartment that can influence right atrial pressure. These factors include left and right heart passive tension curves, the pericardium, the load on the left and right ventricles, mechanical interaction between the lung and the heart, and pleural pressure. The interdependence of these factors is discussed elsewhere in this Seminar.[9]

A cardiac function curve can be determined by observing the effect on cardiac output of increasing the filling of the right atrium. As the right atrium is filled, its transmural pressure increases as a function of its compliance. Heretofore, we have considered only the value of right atrial pressure in relation to atmospheric pressure. If the local pleural pressure acting on the outside of the intact right atrium is assumed to be -3 cm H_2O, we can subtract 3 cm H_2O from the transmural right atrial pressure and obtain a right atrial pressure value relative to atmosphere in the intact system.

In practical terms, the cardiac function curve is obtained by the addition of volume to the heart at a single output load. This is done by increasing mean systemic pressure in steps (Fig. 8B). The cardiac output and right atrial pressure are determined at each of the several levels of mean systemic pressure. The increase in pressure in the right atrium is linked to all of the aforementioned factors. For example, patients on positive pressure ventilation or positive end-expiratory pressure have a higher right atrial pressure in relation to atmosphere at the same transmural right atrial pressure (Fig. 8C). This analysis assumes no change in the cardiac function curve as a result of increased pleural pressure, and mean systemic pressure would have to be increased an equal amount to maintain cardiac output. Figure 8D demonstrates that without the increase in mean systemic pressure, cardiac output would be reduced substantially.

Increased output load on the right heart chamber necessitates greater pressure in these chambers to maintain the flow of blood from the right to the left side. As this pressure increases, the volume in the right heart chambers, and therefore mean transmural right atrial pressure, increases. The pressure-volume relation of the right atrium has not been determined, but a diastolic pressure-volume curve for the canine right ventricle has been measured.[10,11] In Figure 9 the

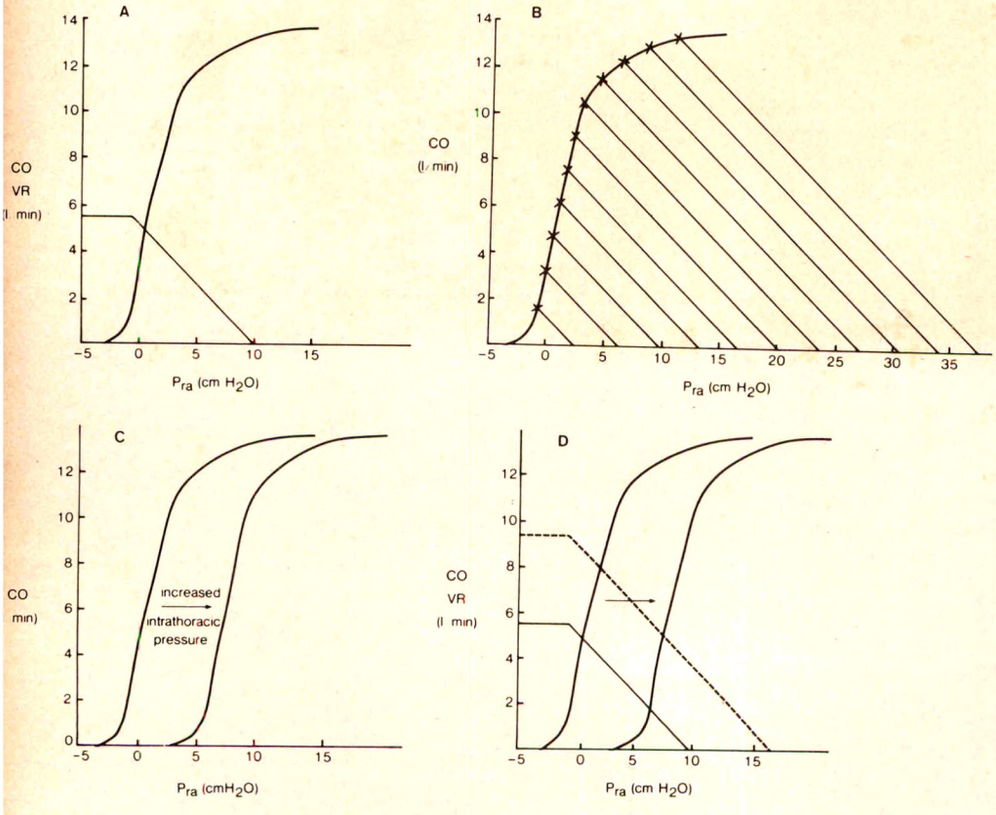

FIGURE 8. A, a venous return (VR) curve and a cardiac function curve are plotted together. The intersection of the two curves determines cardiac output (CO). **B,** the technique for determining a cardiac function curve. Heart filling is increased by a progressive increase in mean systemic pressure; the resulting cardiac output and right atrial pressure (P_{ra}) are plotted. **C,** with no change in cardiac function, an increase in intrathoracic pressure shifts the cardiac function curve to the right. This occurs because at the same right heart volume and the same transmural right atrial pressure, right atrial pressure is increased in relation to atmospheric pressure. **D,** for a parallel shift in the cardiac function curve, mean systemic pressure must be increased to maintain cardiac output.

diastolic compliance of the right ventricle is relatively high; a large change in volume is associated with only a modest change in pressure. If this increase in end-diastolic right ventricular pressure reflects the change in right atrial pressure, then the latter would change relatively little with major changes in right heart volume. In the face of an increased output load, right ventricular volume increases.[10,11] Because this volume change is associated with a small change in end-diastolic right ventricular pressure, and therefore right atrial pressure, only modest increases in mean systemic pressure are necessary to maintain normal cardiac output.

Response to Increased Right Heart Afterload

In respiratory failure, either acute or chronic, there may be an increase in afterload on the right heart. Experiments to obtain data on complete right heart function curves at various loads have not been done. Such experiments might show that changes in contractility may occur in the chronic state that are not present under acute loading conditions. However, it is clear that increased load in the right heart chambers leads to increased pressure in the right atrium if cardiac output is maintained. This implies that mean systemic pressure also must have increased. One of the mechanisms available for increasing mean systemic pressure is retention of fluid to increase vascular stressed volume. Although this can lead to clinical signs of right heart failure, in fact, the right heart chambers may be operating normally but at a higher pressure. Even though in the intact animal or in man, the right heart chambers are part of an interdependent system, useful information about right heart function in response to increased load can be obtained from pressure-volume studies of the right ventricle in isolated hearts.

Figure 9A, redrawn from Maughan et al.,[10] shows that the maximal systolic tension curve and the diastolic tension curve are both linear for a range of total tension of about 10 to 80 mm Hg. In Figure 9B, redrawn from Janicki and Weber,[11] who also studied the isolated dog heart, the curve includes a pressure-volume relation of the right ventricle with the pericardium intact as well as with the pericardium removed, which was the case in the study of Maughan et al.[10] The latter curves differ slightly from those of Maughan et al. in that they are more curvilinear at higher loads. Because heart rate was kept constant by pacing in both studies, changes in stroke volume can be translated directly into changes in cardiac output.

Because cardiac function curves are determined at a fixed load, if a plot is made of stroke volume versus end-diastolic right ventricular pressure at a given load, a curve equivalent to the cardiac function curve is generated. Stroke volume-right ventricular end-diastolic pressure points at a given right ventricular pressure load can be obtained from the data in Figure 9. This is done by drawing a line perpendicular to a given right ventricular pressure. Two such lines can be seen in Figure 9A, one at 20 and one at 40 mm Hg. At the point that this perpendicular line crosses the maximal systolic tension curve, a line parallel to the ordinate is drawn. The intersection of this new line and the diastolic tension curve defines the minimal volume necessary for the ventricle to develop the desired tension. At this point, the stroke volume would be zero and end-diastolic right ventricular pressure defined. Figure 9A shows that, as the load increases, the right ventricular end-diastolic pressure demonstrated in this way increases. However, for equal increments in stroke volume at each load, the change in right ventricular and diastolic pressures would

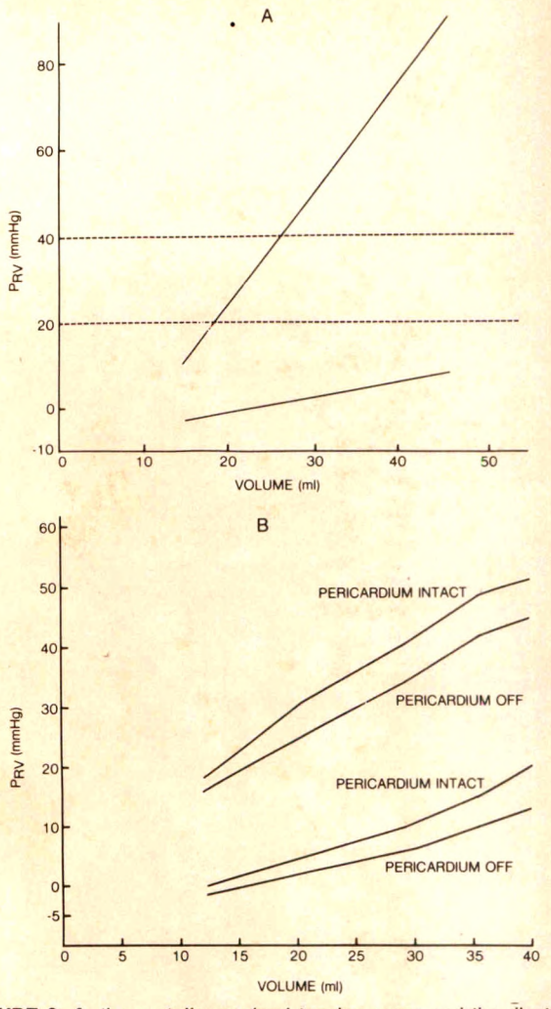

FIGURE 9. A, the systolic maximal tension curve and the diastolic tension curve, redrawn from Maughan et al.[10] The **dashed lines** identify the point at which a right ventricular pressure (P_{RV}) of 20 or 40 mm Hg crosses the maximal tension curve. It can be seen that the state of diastolic filling necessary for the right ventricle to reach the greater developed tension is increased. Therefore, right ventricular diastolic pressure is greater. However, if stroke volume were to increase at either load, the change in right ventricular end-diastolic pressure would be the same. The diastolic curve also shows that as right ventricular volume increases to about 45 ml, the end-diastolic pressure in the right ventricle increases to only about 5 mm Hg. **B,** right ventricular pressure-volume curves with the pericardium intact or removed. These curves are redrawn from Janicki and Weber.[11]

be identical. When the relation between stroke volume and right ventricular end-diastolic pressure obtained in this way is plotted (Fig. 10), changes in right ventricular afterload are shown to cause a parallel shift in the function curve to the right. This parallel shift is analogous to the effect of increased pleural pressure described earlier. Therefore, as afterload in the right ventricle increases within the limits of these studies, cardiac output can be maintained by increasing mean systemic pressure (Fig. 8D).

Figure 9 also shows that, as load increases, end-diastolic volume increases if stroke volume is constant. These changes would lead to a larger end-systolic volume and a reduced ejection fraction, but no change in the slope of the cardiac function curve. A potential limit

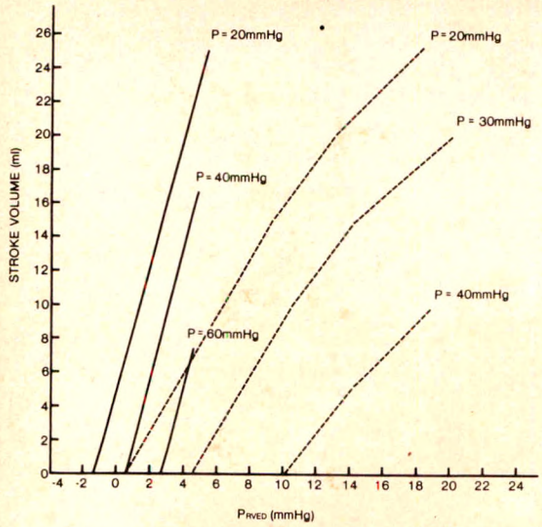

FIGURE 10. This figure, derived from data presented in Figure 9, shows the relation between right ventricular end-diastolic pressure (P_{RVED}) and stroke volume at various right ventricular loads identified by the pressure (P) noted at the top of each curve. The data from which these curves were derived were obtained at a constant heart rate. Therefore, changes in stroke volume can be taken as changes in cardiac output. If right ventricular end-diastolic pressure can be taken as similar to right atrial pressure, then the relation displayed is similar to cardiac function curves. With increasing load, the curves exhibit a parallel shift to the right and down.

to the maintenance of cardiac output would occur if these stroke volume–right ventricular end-diastolic pressure curves exhibited a plateau. However, an increase in heart rate could overcome this. Indeed, in a study by Stool et al.,[12] when stroke volume decreased in intact dogs given acute increases in right heart output load, heart rate increased and cardiac output was maintained.

This analysis helps explain why cardiac glycosides might not be of value in the management of some patients with cor pulmonale. The cardiac glycosides would be expected to increase the slope of the cardiac function curve, but because these curves are already relatively steep and may only be shifted to the right, improvement in right atrial pressure at a given cardiac output would be modest. This effect may be more than balanced by a decrease in mean systemic pressure in the absence of hypervolemia, because cardiac glycosides have been shown to increase unstressed vascular volume in dogs.[13] This could result in a decrease in the gradient between mean systemic and right atrial pressures and a reduction in venous return and, therefore, in cardiac output.

This analysis also points out a potential danger in the overvigorous use of diuretic agents in the management of patients with cor pulmonale. Excessive use of such agents could lead to a significant decrease in mean systemic pressure resulting from a decrease in intravascular volume. Ankle edema might be alleviated, but the cost might be a reduction in cardiac output.

Conclusions

We have analyzed the circulation in terms of a closed loop system in which cardiac output cannot exceed venous return. Venous return is determined by the difference between mean systemic and right atrial pressures at a constant resistance to venous return. Mean systemic pressure can be changed by altering the vascular stressed volume or systemic vascular compliance. Changes in right atrial pressure are more complex. For the purposes of venous return, since mean systemic pressure is determined in relation to atmospheric pressure, right atrial pressure must be expressed in relation to atmospheric pressure. Right atrial pressure is increased in relation to atmospheric pressure by factors such as positive pressure ventilation, positive end-expiratory pressure and increased volume in the right heart chambers secondary to increased afterload, such as might occur with acute or chronic respiratory failure. Through interdependent mechanisms, right atrial pressure also may be increased by pericardial effusion or left heart dysfunction. As right atrial pressure increases, mean systemic pressure must increase to maintain a normal cardiac output, and these changes may lead to signs of right heart failure. For these signs to occur, the right heart chambers need not have a depressed function curve, but merely be shifted to the right on the cardiac output-right atrial pressure axis.

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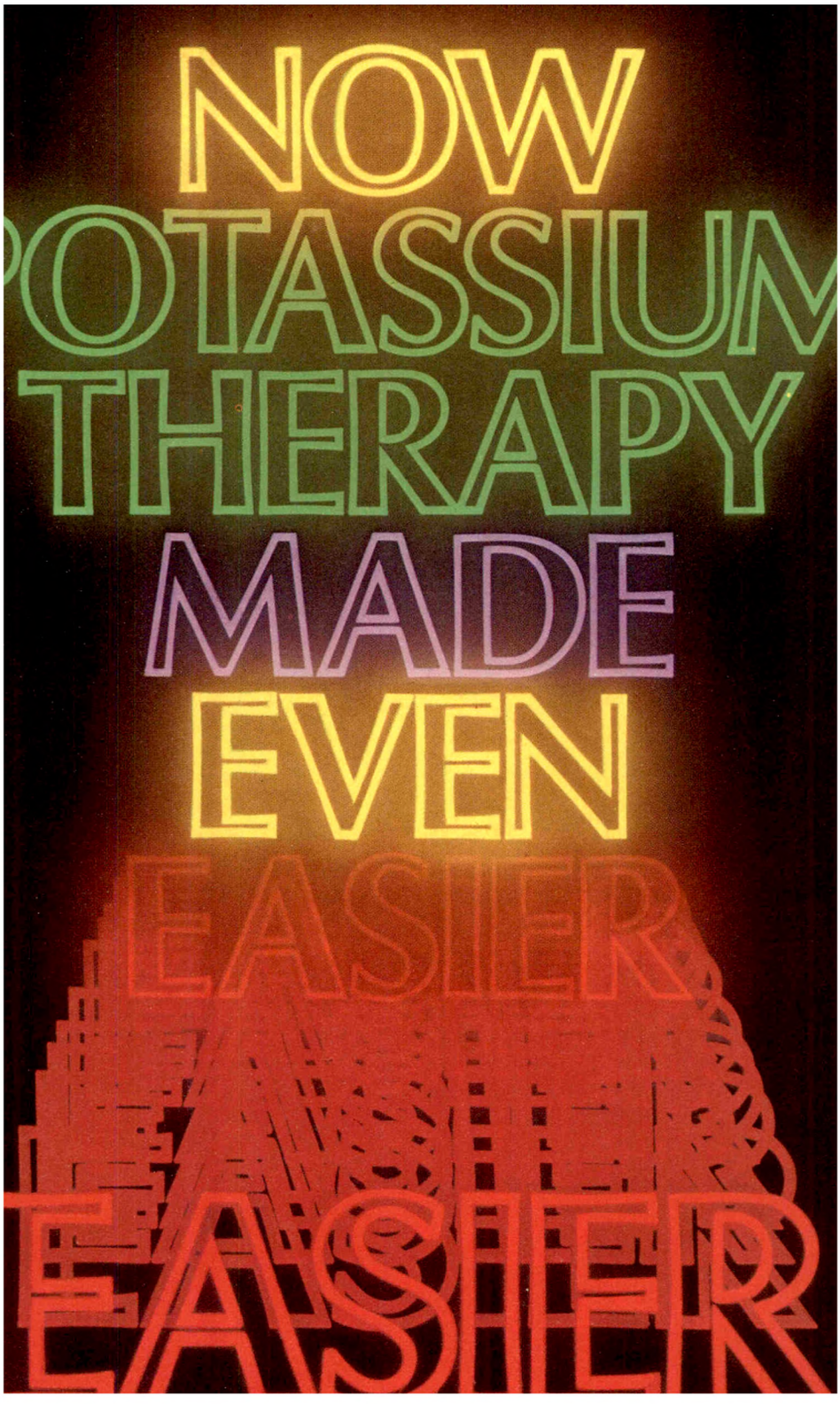
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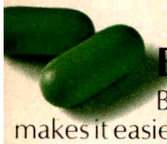

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Brief Summary

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For therapeutic use in patients with hypokalemia with or without metabolic alkalosis, in digitalis intoxication and in patients with hypokalemic familial periodic paralysis.

For the prevention of potassium depletion when the dietary intake is inadequate in the following conditions: Patients receiving digitalis and diuretics for congestive heart failure; hepatic cirrhosis with ascites, states of aldosterone excess with normal renal function, potassium-losing nephropathy, and with certain diarrheal states.

The use of potassium salts in patients receiving diuretics for uncomplicated essential hypertension is often unnecessary when such patients have a normal dietary pattern. Serum potassium should be checked periodically, however, and if hypokalemia occurs, dietary supplementation with potassium-containing foods may be adequate to control milder cases. In more severe cases supplementation with potassium salts may be indicated.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia since a further increase in serum potassium concentration in such patients can produce cardiac arrest. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g., spironolactone, triamterene).

Wax-matrix potassium chloride preparations have produced esophageal ulceration in certain cardiac patients with esophageal compression due to enlarged left atrium. Potassium supplementation, when indicated in such patients, should be with a liquid preparation.

All solid dosage forms of potassium chloride supplements are contraindicated in any patient in whom there is cause for arrest or delay in tablet passage through the gastrointestinal tract. In these instances, potassium supplementation should be with a liquid preparation.

Warnings: Hyperkalemia—In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. This occurs most commonly in patients given potassium by the intravenous route but may also occur in patients given potassium orally. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in patients with chronic renal disease, or any other condition which impairs potassium excretion, requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Interaction with Potassium Sparing Diuretics—Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g., spironolactone or triamterene) since the simultaneous administration of these agents can produce severe hyperkalemia.

Gastrointestinal Lesions—Potassium chloride tablets have produced stenotic and/or ulcerative lesions of the small bowel and deaths. These lesions are caused by a high localized concentration of potassium ion in the region of a rapidly dissolving tablet, which injures the bowel wall and thereby produces obstruction, hemorrhage, or perforation. Kaon Cl™-10 mEq (potassium chloride) is a wax-matrix tablet formulated to provide a controlled rate of release of potassium chloride and thus to minimize the possibility of a high local concentration of potassium ion near the bowel wall. While the reported frequency of small bowel lesions is much less with wax-matrix tablets (less than one per 100,000 patient years) than with enteric-coated potassium chloride tablets (40-50 per 100,000 patient years) cases associated with wax-matrix tablets have been reported both in foreign countries and in the United States. In addition, perhaps because the wax-matrix preparations are not enteric-coated and release potassium in the stomach, there have been reports of upper gastrointestinal bleeding associated with these products. The total number of gastrointestinal lesions remains less than one per 100,000 patient years. Kaon Cl-10 mEq should be discontinued immediately and the possibility of bowel obstruction or perforation considered if severe vomiting, abdominal pain, distention, or gastrointestinal bleeding occurs.

Metabolic Acidosis—Hypokalemia in patients with metabolic acidosis should be treated with an alkalinizing potassium salt such as potassium bicarbonate, potassium citrate, potassium acetate, or potassium gluconate.

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, the physician should bear in mind that acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient.

Adverse Reactions: The most common adverse reactions to oral potassium salts are nausea, vomiting, abdominal discomfort and diarrhea. These symptoms are due to irritation of the gastrointestinal tract and are best managed by diluting the preparation further, taking the dose with meals, or reducing the dose.

The most severe adverse effects are hyperkalemia (see Contraindications, Warnings and Overdosage) and gastrointestinal obstruction, bleeding or perforation (see Warnings).

Overdosage: The administration of oral potassium salts to persons with normal excretory mechanisms for potassium rarely causes serious hyperkalemia. However, if excretory mechanisms are impaired or if potassium is administered too rapidly intravenously, potentially fatal hyperkalemia can result (see Contraindications and Warnings). It is important to recognize that hyperkalemia is usually asymptomatic and may be manifested only by an increased serum potassium concentration and characteristic electrocardiographic changes (peaking of T-waves, loss of P-wave, depression of S-T segment, and prolongation of the QT interval). Late manifestations include muscle-paralysis and cardiovascular collapse from cardiac arrest.

Treatment measures for hyperkalemia include the following:

1. Elimination of foods and medications containing potassium and of potassium-sparing diuretics.
2. Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml.
3. Correction of acidosis, if present, with intravenous sodium bicarbonate.
4. Use of exchange resins, hemodialysis, or peritoneal dialysis.

In treating hyperkalemia, it should be recalled that in patients who have been stabilized on digitalis, too rapid a lowering of the serum potassium concentration can produce digitalis toxicity.

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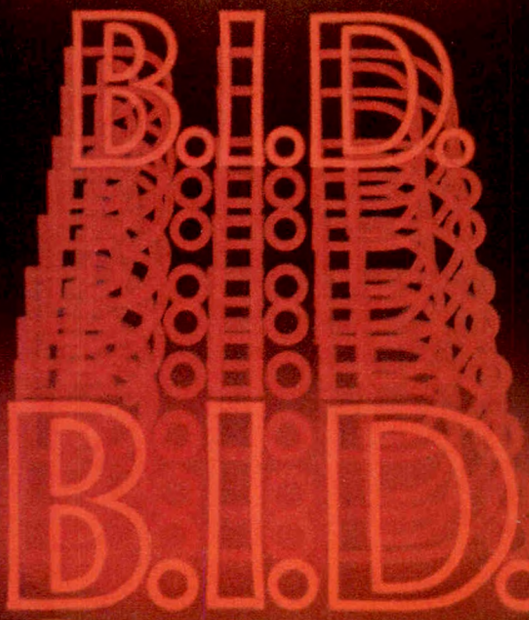

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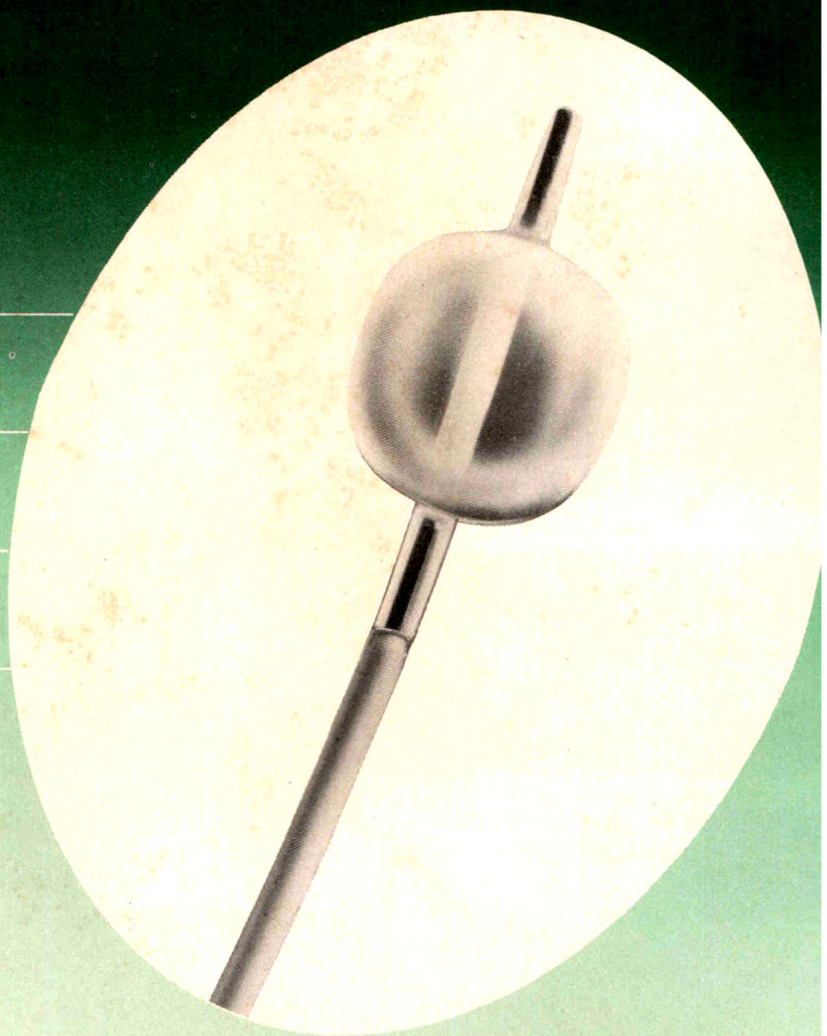

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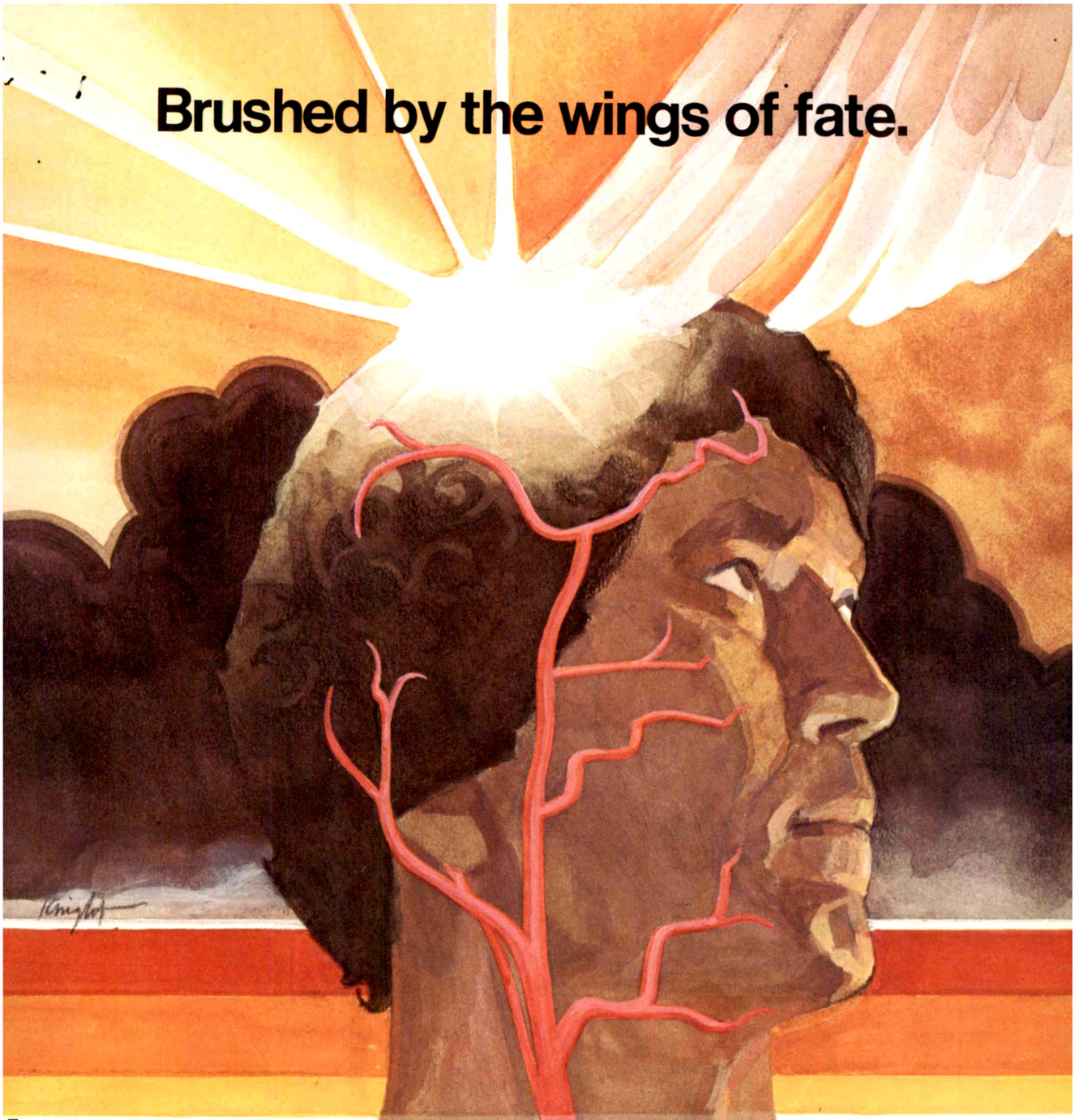

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Observations on Spontaneous Termination of Atrioventricular Nodal Reentrant Tachycardia

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Unusual mechanisms of spontaneous termination of atrioventricular (A-V) nodal reentrant tachycardia were observed in two patients during programmed electrical stimulation of the heart. In both patients the mechanism of termination was based on the use of another reentrant pathway than the one used during tachycardia. This pathway was located extranodally in one patient and intranodally in the other. The observations illustrate some of the complexities of reentry in the human heart and how they can play a role in spontaneous termination of A-V nodal tachycardia.

Observations in the animal heart[1,2] and data from programmed electrical stimulation in the human heart[3,4] support reentry as the most common mechanism for atrioventricular (A-V) nodal tachycardia. Reentry requires the presence of two interconnected pathways having different electrophysiologic properties. Termination of reentry occurs when refractory tissue halts the circulating impulse somewhere in the reentrant pathways. In this study we report observations on spontaneous termination of tachycardia in two patients with A-V nodal tachycardia, emphasizing how a third pathway that is connected to the reentry circuit can result in refractoriness in the reentry circuit and termination of the arrhythmia.

Methods

Patient 1 was a 20 year old man with A-V nodal tachycardia at a rate of 200/min. Patient 2 was a 70 year old man with A-V nodal tachycardia at a rate of 150/min. After the patients gave informed consent, they underwent an electrophysiologic study in the resting postabsortive, nonsedated state. Neither patient was receiving medication at the time of study. With use of the femoral approach, catheters were placed for both stimulation and recording of intracardiac electrograms in the apex of the right ventricle, the bundle of His region, the high right atrium and the coronary sinus. Our stimulation protocol has previously been described.[5] Both patients underwent a complete study. Only relevant data will be presented.

Criteria for the diagnosis of A-V nodal reentrant tachycardia: The diagnosis of A-V nodal tachycardia was based largely on exclusion of the use of an accessory A-V pathway as the retrograde limb of the tachycardia circuit and exclusion of an atrial site of origin of the tachycardia. The exclusion criteria were as follows: (1) Supraventricular tachycardia inducible by atrial premature beats related to A-V nodal delay.[3–4,6] (2) Simultaneous activation of atria and ventricles during tachycardia.[6] (3) H-A interval during tachycardia independent of H-V interval or bundle branch block pattern. (4) Persistence of tachycardia during A-V block distal to the bundle of His area (Patient 1). (5) Inability to advance atrial activation during tachycardia by ventricular premature beats given at the time of refractoriness of the bundle of His.[7] (This observation does not exclude the presence of an accessory A-V pathway, but the opposite finding would prove its presence.[6]) (6) Ventriculoatrial conduction during ventricular pacing and after ventricular premature beats related to depolarization of the bundle of His[8] and subnodal delay of ventricular premature beats.[9] (7) Similar atrial activation

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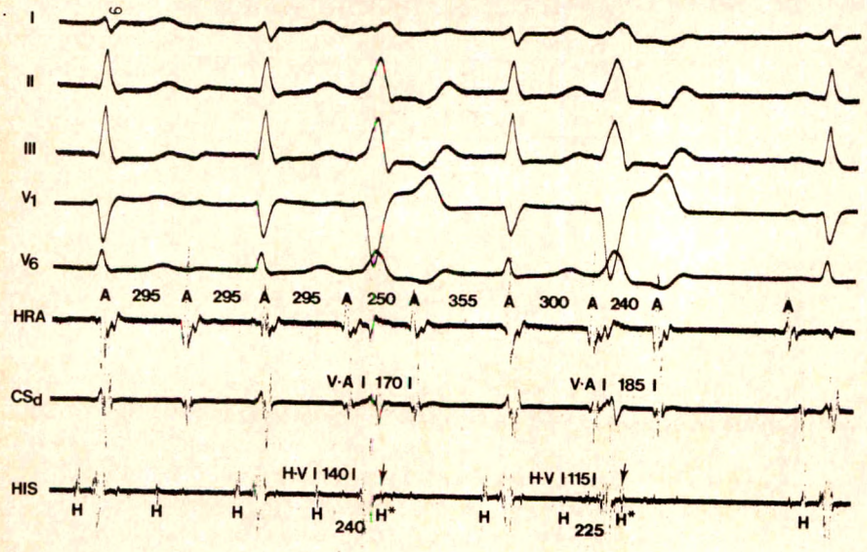

FIGURE 1. Case 1. Atrioventricular (A-V) nod tachycardia originally showing 2:1 block distal the bundle of His. After recovery of 1:1 A-V co duction over the right bundle branch (third QR complex, with a left bundle branch block confi uration) subsequent atrial activation is advance When this pattern is repeated (fifth QRS comple tachycardia is terminated. Indicated are th tachycardia cycle length in ms, the H-V interv preceding the widened QRS complexes and th V-A interval following these widened QRS com plexes as measured in the distal coronary sinu (CSd) lead for clarity. **Arrows** point to possibl retrograde His bundle potentials labeled H*. Se text and Figure 2 for explanation. Leads I, II, III, V and V_6 were simultaneously recorded with a hig right atrial (HRA), a distal coronary sinus and a Hi bundle electrogram.

pattern during tachycardia and after retrograde conduction during ventricular pacing, suggesting that in both circumstances the same pathway was used for retrograde conduction.

Conventional definitions were used for refractory periods. The A-V nodal conduction curve was considered discontinuous if increasing the prematurity of the test pulse (atrial or ventricular) by 10 ms resulted in a sudden increase in A-V nodal conduction time by 50 ms or more. This sudden unexpected increase in A-V nodal conduction time of a premature beat suggests a shift in conduction from a fast to a slow A-V nodal pathway.[1–4,6,7]

Results

Patient 1: Termination of A-V nodal tachycardia by bundle branch reentry: A-V nodal tachycardia with a cycle length of 295 ms originally showed 2:1 block distal to the bundle of His (Fig. 1). During recovery of 1:1 A-V conduction the first QRS complex shows a prolonged H-V interval (140 ms) and a complete left bundle branch block configuration. This QRS complex is followed by atrial activation with the sequence of atrial activation similar to the one recorded during tachycardia and occurring 45 ms earlier than expected, indicating that the atrial complex is not the result of regular impulse formation during tachycardia. The fifth QRS complex during tachycardia again shows a left bundle branch block pattern, but with an H-V interval of 115 ms. This QRS complex is followed by atrial activation occurring earlier than expected. After this atrial complex the tachycardia terminates.

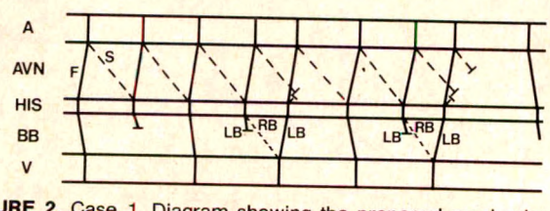

FIGURE 2. Case 1. Diagram showing the proposed mechanism of termination of tachycardia in Figure 1. A = atrium; AVN = atrioventricular node; BB = bundle branches; F = fast A-V nodal pathway; LB = left bundle branch; RB = right bundle branch; S = slow A-V nodal pathway; V = ventricle. See text.

The H-A interval stays the same in spite of changing H-V intervals during the aberrant complexes, or in spite of block of conduction to the ventricles at a site distal to the bundle of His. We postulate (Fig. 2) that during left bundle branch block the impulse traveling to the ventricles over the right bundle branch is able to invade in retrograde fashion the left bundle branch and reenters the A-V node. Retrograde conduction over the fast A-V nodal pathway allows premature activation of the atrium.

In Figures 1 and 3 possible retrograde His bundle potentials following the aberrant QRS complexes are identified. It was considered that they should precede the atrial echo by 80 ms or more (the H-A interval during tachycardia). An inverse relation is observed between the H-V interval and the V-H interval after the aberrant QRS complexes, (the V-H interval measures 100 ms after an H-V interval of 140 ms, and 110 ms after an H-V interval of 115 ms). The V-A interval following the aberrant complexes (as measured from the ventriculogram in the distal coronary sinus lead to the onset of atrial activation in the same lead) changes in the absence of changes in the bundle branch block pattern. This observation suggests that a free wall bypass tract is not the pathway used for retrograde conduction. Tachycardia is terminated depending on the retrograde and anterograde input in the A-V nodal pathways as reflected by the H-H and A-A intervals. After the first aberrant QRS complex the H-H interval measures 240 ms (Fig. 1) and the A-A interval 250 ms. This results in some degree of concealed penetration of the impulse in the slow A-V nodal pathway (Fig. 2) and collision with the anterograde front within this pathway, whereas retrograde conduction to the atria takes place over the fast A-V nodal pathway. The atrial complex is conducted in anterograde manner with a transient increase in the slow pathway conduction time. However, after the second aberrant QRS complex both the H-H interval (225 ms) and the A-A interval (240 ms) are shorter (Fig. 1). This shortening results in a major degree of concealed penetration of the impulse in the slow pathway that, in combination with a shorter A-A interval, results in block of impulse conduction in the slow pathway and termination of tachycardia (Fig. 1 and 2).

Occasionally right bundle branch block was observed during the change from 2:1 to 1:1 A-V conduction. This also resulted in the echo phenomenon (Fig. 3). However, because of the retrograde and anterograde input in the A-V nodal pathways

(H-H interval 240 ms and A-A interval 260 ms after the aberrant QRS complex) a fully compensatory pause followed and tachycardia continued. In this patient atrial premature beats delivered during atrial pacing at a basic cycle length of 600 ms did not result in aberrant conduction to the ventricles, the shortest attainable H_1-H_2 interval measuring 330 ms.

Patient 2. Termination of A-V nodal tachycardia by a sudden change in another anterograde A-V nodal pathway: An A-V nodal tachycardia with anterograde conduction over a "slow" pathway and retrograde conduction over a "fast" pathway (Fig. 4) was terminated spontaneously by a cycle that (1) was 115 ms shorter than the cycles seen during tachycardia, and (2) was not followed by retrograde conduction to the atria. This mode of spontaneous termination was repeatedly observed and probably can be explained by the A-V nodal conduction curves shown in Figure 5. During single test stimulation of the right atrium at a basic cycle length of 500 ms, several discontinuities in the A_2-H_2 curve are seen. This was also during stimulation with a basic cycle length of 460 ms. These findings support the presence of either more than one "slow" pathway or delay in a final common pathway. The former hypothesis is supported by the fixed H to atrial echo interval at the time of initiation of tachycardia irrespective of the preceding A-H interval. If a final common pathway were responsible for delay in conduction to the His bundle and the "jumps" in the conduction curve, a changing relation between His bundle activation and atrial echo would have been observed.

We postulate that in this patient tachycardia terminates spontaneously because of conduction over a "slow" pathway that is not slow enough to overcome retrograde refractoriness of the "fast" retrograde pathway (Fig. 6). Although the anterograde and retrograde refractory periods of the fast pathway need not be equal, the anterograde refractory period of the fast pathway measured 290 ms and the H-H interval terminating tachycardia measured 280 ms (a lesser value). After initiation of tachycardia (Fig. 6), we postulate a decreasing concealment in the third pathway that is finally relieved, allowing anterograde conduction over this pathway, the impulse colliding in the slow pathway with the anterograde front and blocking in the fast pathway because it is entering at a time when the pathway is still refractory.

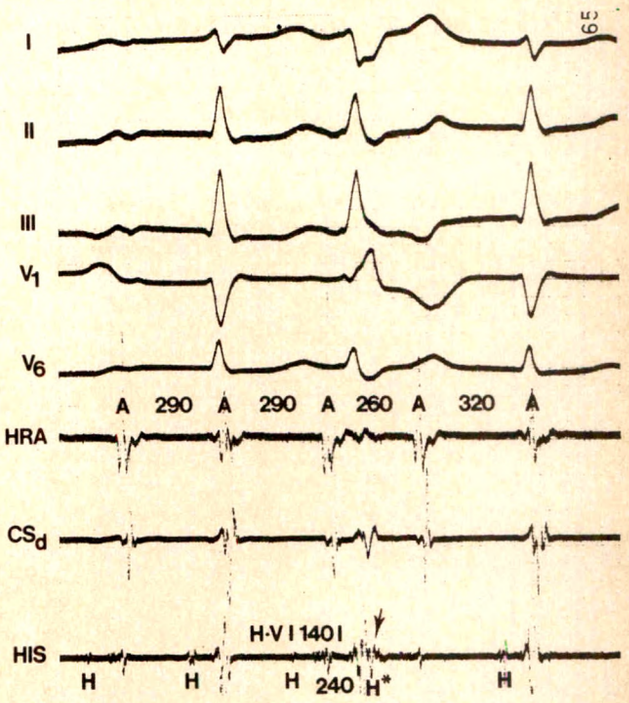

FIGURE 3. Case 1. A-V nodal tachycardia with 2:1 block distal to the bundle of His showing recovery of conduction over the left bundle branch (second QRS complex, with a right bundle branch block configuration). Subsequent atrial activation is advanced but tachycardia continues. Same leads and labeling as in Figure 1. See text.

Discussion

A third pathway with bundle branch reentry: In these two patients the findings strongly suggest that reentry into the tachycardia circuit over a third pathway was responsible for termination of the arrhythmia. This third pathway was not involved in the reentrant pathways during initiation and perpetuation of tachycardia. Atrial echo beats based on reentry over the bundle branches have been demonstrated to occur.[10–12] As in those studies, the atrial echoes in our Patient 1 required the presence of block in one of the bundle branches and sufficient delay in conduction over the other bundle branch to complete a reentrant cycle. The time of arrival of the impulse in the A-V nodal pathways (in both anterograde and retrograde directions as reflected by the H-H and A-A intervals following the aberrant complex) was crucial for termination of the reentrant movement. It seems unlikely that the widened QRS complexes represented ventricular extrasystoles occurring late in diastole. Ventricular premature beats were not observed to occur spontaneously throughout the investigation and, as shown, advancement of subsequent atrial activation was observed during both left and right bundle branch block-shaped QRS complexes. The range of H-V intervals preceding these widened QRS complexes is in keeping with previous clinical observations[10] and the results of experimental studies.[12]

An inverse relation between H-V and V-H intervals during the widened QRS complexes was demonstrated in our Patient 1, supporting the concept of bundle branch reentry.[10] In this patient we could exclude the presence of an extranodal accessory pathway. Depolarization of the bundle of His occurred twice during H-H intervals of 240 to 225 ms (Fig. 1 and 3). Experimental studies[12] have shown that retrograde depolarization of the His bundle can occur as soon as 160 ms after its anterograde depolarization. The observation of bundle branch block with slow conduction over the contralateral branch with advancement of subsequent atrial activation makes bundle branch reentry the most plausible explanation for termination of tachycardia in this patient. Unfortunately, bundle branch block and atrial echoes were not observed during atrial premature beats delivered during pacing of the right atrium at a basic cycle length of 600 ms. Their absence might have occurred because the H-H interval of 300 ms during tachycardia could result in concealment in the bundle branch system, allowing development of bundle branch block patterns, whereas such concealed conduction presumably did not occur during atrial pacing at a basic cycle length of 600 ms.

Anterograde intranodal conduction over a third A-V nodal pathway: In Patient 2 a sudden shortening in the cycle length of reentry was followed by termina-

tion of tachycardia. The degree of shortening is too great to be accounted for by a sudden change in autonomic tone. The most attractive hypothesis to explain this phenomenon is anterograde intranodal conduction over a different A-V nodal pathway with slow conduction time. The finding of several discontinuities in the A-V nodal conduction curve might support this theory. It is of interest that the A-H interval after the first break in the A-V nodal conduction curve is similar to the A-H interval before termination of tachycardia, measuring 230 and 215 ms, respectively (Fig. 4 and 5). We cannot exclude the possibility that a His bundle extrasystole was responsible for termination of tachycardia and the apparent shortening of the A-H interval. Also we do not know the validity of comparing the A-H interval terminating tachycardia with the A-H interval after the

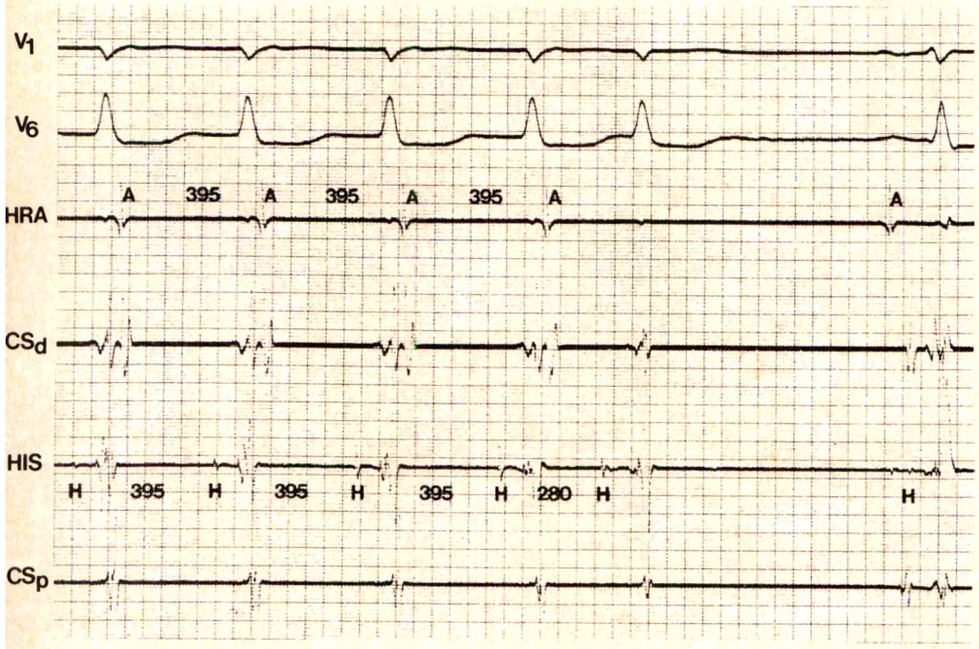

FIGURE 4. Case 2. A-V nodal tachycardia with a cycle length of 395 ms. Tachycardia terminates after sudden shortening in the H-H interval by 115 ms, corresponding to 115 ms shortening in the A-H interval. This repeatedly observed phenomenon was not preceded by any changes in time relations during the tachycardia. Leads V_1 and V_6 were simultaneously recorded with four endocavitary electrograms. CSp = Proximal coronary sinus electrogram.

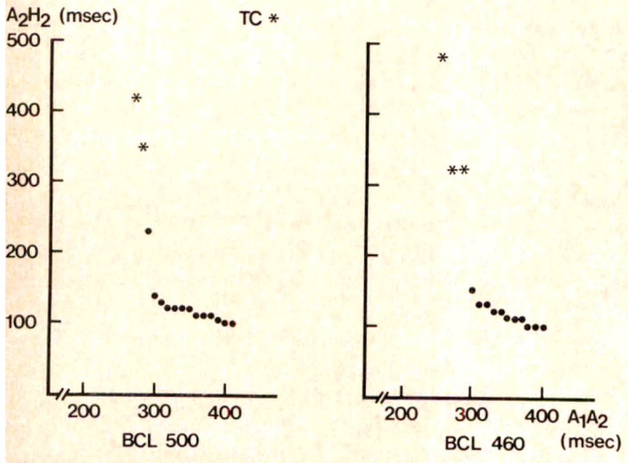

FIGURE 5. Case 2. Relation between the A_1–A_2 intervals (**abscissa**) during pacing of the high right atrium at basic cycle lengths of 500 and 460 ms. Three discontinuities in the A-V nodal conduction curve were observed during atrial pacing with a basic cycle length of 500 ms (**left**), and two when the basic cycle length of pacing was decreased to 460 ms (**right**). TC = atrial premature beats initiating tachycardia.

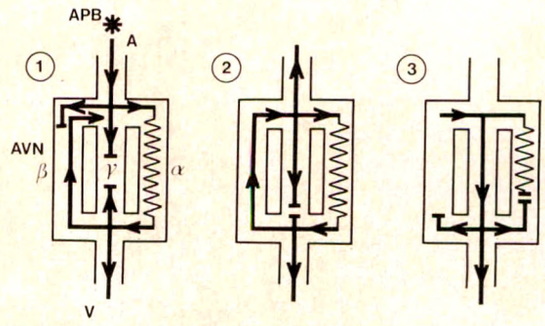

FIGURE 6. Case 2. Diagram illustrating the proposed mechanism of termination of tachycardia as observed in Figure 4. α, β and γ represent three A-V nodal pathways. In panel 1, an atrial premature beat (APB) is blocked in pathways β and γ and initiates tachycardia after anterograde conduction over pathway α (the slowest conducting pathway) and retrograde conduction over pathway β (the fastest pathway). Pathway γ is maintained refractory because of concealed anterograde and retrograde penetration of impulses during tachycardia. In panel 2, decreasing concealed penetration in pathway γ in the retrograde direction is postulated. In panel 3, after recovery of conduction in the anterograde direction in pathway γ the impulse is conducted to the ventricles with a shorter than expected A-H interval. The impulse blocks in pathway β because of refractoriness of this pathway, and collides in pathway α with the anterograde impulse, resulting in termination of tachycardia. Abbreviations as in Figure 2.

first break in the A-V nodal conduction curve of the left graph from Figure 5 when cycle lengths are different. However, we believe that the reproducibility of our observations, the several discontinuities in the A-V nodal conduction curve and the mode of termination of tachycardia suggest the availability of several A-V nodal pathways. The availability of several A-V nodal pathways has already been advanced from animal studies.[2] In Patient 2 a similar A-V nodal conduction time was observed not to initiate or to terminate tachycardia, thus suggesting the use of a third A-V nodal pathway that was not slow enough to overcome refractoriness of the retrograde A-V nodal pathway used during tachycardia.

Implications: In these two patients, sudden unexpected conduction over another reentrant pathway accounted for termination of the arrhythmia. Why these pathways were suddenly able to conduct is difficult to explain. Although, the factors leading to the new reentrant pathway terminating tachycardia could be recognized in Patient 1, they remain unclear in Patient 2. One can speculate that differences in degree of concealed penetration of the impulse in potential reentrant circuits or changes in refractoriness and conduction velocity during tachycardia might have played a role. However, our present methods of investigation in the intact human heart are not refined enough to uncover most of these complex mechanisms.

Acknowledgment

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Prolapsed Left Atrium Behind the Left Ventricular Posterior Wall: Two Dimensional Echocardiographic and Angiographic Features

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Left atrial enlargement can usually be detected accurately using M mode echocardiography. However, in the presence of heart disease, asymmetric enlargement may lead to inaccurate assessment of left atrial size and shape. Pericardial effusion can usually be diagnosed on the basis of characteristic M mode echocardiographic findings. However, false positive patterns sometimes occur with the use of this single dimensional technique. Three patients with a greatly enlarged left atrium are described whose M mode echocardiogram suggested significant posterior pericardial fluid accumulation. In each patient, two dimensional echocardiography detected portions of a huge left atrium that prolapsed behind the left ventricular posterior wall and mimicked an isolated posterior pericardial effusion. In one case a right anterior oblique left ventricular cineangiogram suggested the presence of a ventricular septal defect or a false aneurysm of the left ventricle due to the prolapsed left atrium. Because two dimensional echocardiography can provide accurate spatial orientation with visualization of intracardiac structures in relation to one another in real time, it can identify the presence of left atrial prolapse and play an important role in the differential diagnosis of isolated echo-free spaces behind the left ventricle detected with M mode echocardiography.

Echocardiography has been shown to be an accurate noninvasive technique for determining left atrial size[1–4] and detecting the presence of pericardial fluid.[5–8] However, with single dimensional M mode echocardiography, asymmetric left atrial enlargement can lead to inaccurate estimates of left atrial size.[9,10] Furthermore, false positive diagnoses of excessive posterior pericardial fluid accumulations have been noted with the use of M mode echocardiography in a variety of situations.[7] Two dimensional echocardiography is helpful in establishing the true nature of these false positive diagnoses in many instances.[8,11]

The purposes of this study are (1) to report the two dimensional echocardiographic features of left atrial prolapse behind the posterior wall of the left ventricle, which may occur in the presence of a huge left atrium and may mimic the presence of a posterior pericardial effusion, and (2) to report the left ventricular cineangiographic features that in one case suggested the presence of a ventricular septal defect or false aneurysm of the left ventricle.

Methods

Echocardiography: Routine M mode echocardiography was performed in three adult patients with suspected mitral valve disease. The transducer was placed along the left sternal border in the third to fourth intercostal space and angled to record portions of the mitral valve. The transducer was then angled inferiorly and laterally to record echoes from the left ventricular cavity and superiorly and medially to record echoes from the aortic root and left atrium. M

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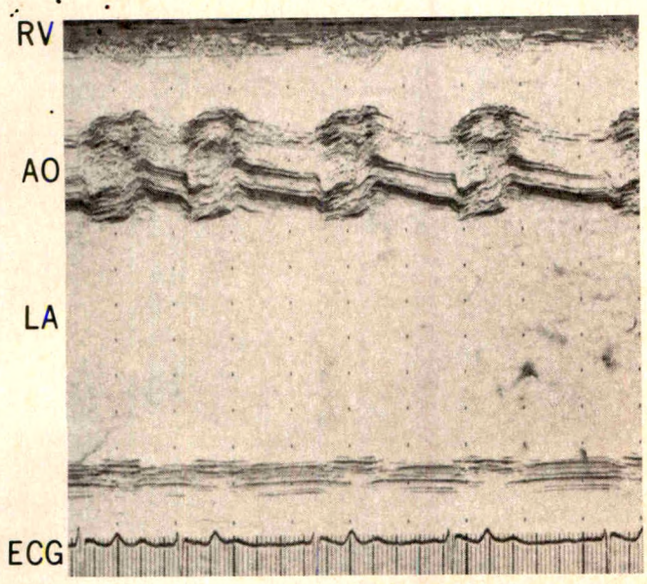

FIGURE 1. Case 1. M mode echogram of the aortic root (AO) demonstrating an anatomically abnormal aortic valve and a huge left atrium (LA) (75 mm). ECG = electrocardiogram; RV = right ventricle.

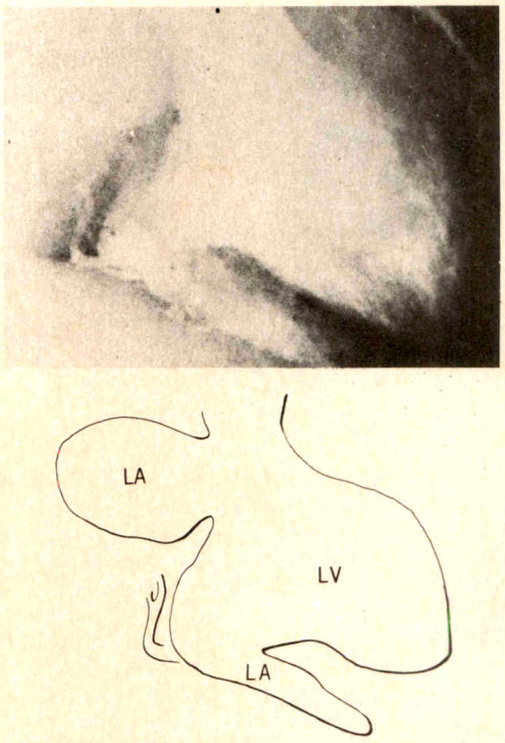

FIGURE 3. Case 1. A representative frame of the right anterior oblique left ventricular cineangiogram taken near end-diastole (**top**) and an artist's reconstruction of the frame (**bottom**). LA = left atrium; LV = left ventricle.

mode tracings were performed with a commercially available Picker 80-C ultrasonoscope with a 2.25 megahertz piezoelectric transducer focused at 7.5 cm. Examinations were recorded on light-sensitive paper using a strip chart recorder.

Sector scan echocardiograms were obtained using a Picker 80-C cardiac imager with a 2.25 megahertz transducer mechanically swept through a 60° arc at 300 sweeps/s. A long axis view of the heart was obtained by positioning the transducer in the third to fourth intercostal space to the left of the sternum and directing the plane of the sweep through the aortic root, the left atrium, the mitral valve and the left ventricle. A transverse view was obtained by rotating the transducer clockwise approximately 90°. Patients were initially placed in a supine position and later in the left lateral decubitus position for both M mode and two dimensional examinations.

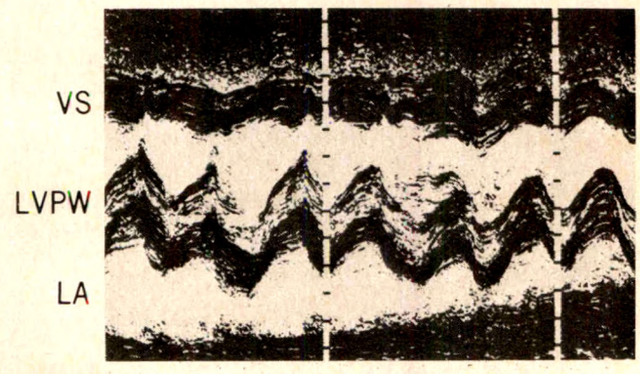

FIGURE 2. Case 1. M mode echocardiogram demonstrating an echo-free posterior space behind the left ventricle due to a prolapsed portion of a huge left atrium (LA). This finding is indistinguishable from that of posterior pericardial effusion. LVPW = left ventricular posterior wall; VS = ventricular septum.

These methods have been described by Nanda and Gramiak.[12]

Cineangiography: Left ventricular cineangiography was performed in the 30° right anterior oblique projection (Cases 1 and 3) and anterior and lateral biplane projections (Case 2) with injection of Renografin® 76. Filming was performed at 60 frames/s.

Case Reports

Case 1: A 65 year old woman with symptoms of congestive heart failure was referred for cardiac evaluation. The findings on physical examination, chest roentgenography and electrocardiography were compatible with mitral insufficiency. An M mode echocardiogram revealed rheumatic mitral valve disease, an anatomically abnormal aortic valve and a markedly enlarged left atrium measuring 75 mm (Fig. 1). An isolated echo-free space was noted behind the left ventricular posterior wall (Fig. 2), suggesting the presence of pericardial effusion. Cardiac catheterization revealed 2+ mitral regurgitation with an enlarged left atrium and no significant mitral valve diastolic gradient. Contrast material was also noted in an unusual location behind the left ventricle outside the confines of the left ventricular cavity (Fig. 3). This angiogram suggested the presence of either a ventricular septal defect or a false aneurysm of the left ventricle. Subsequent review of the right heart oxygen saturation levels revealed no oxygen step-up in the right heart chambers.

Two dimensional echocardiography was then performed. The longitudinal scan best demonstrated a huge left atrium that prolapsed behind the left ventricular posterior wall, ac-

FIGURE 4. Case 1. Two dimensional echocardiogram (**left**) and an artist's reconstruction (**right**). The echocardiogram is a longitudinal scan of the left ventricle demonstrating a huge left atrium (LA) prolapsing behind the left ventricle (LV). PV = prosthetic mitral valve; VS = ventricular septum.

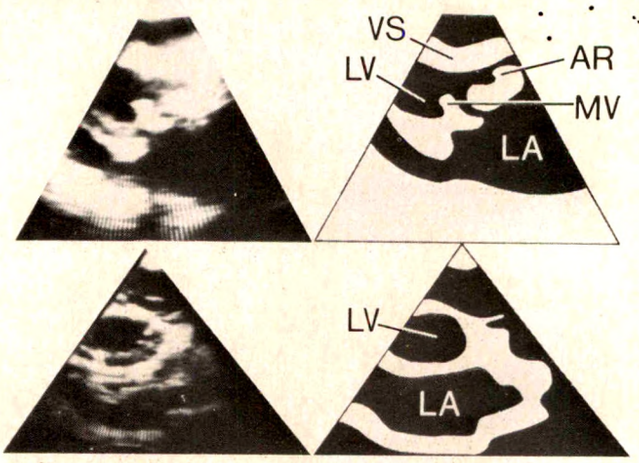

FIGURE 5. Case 2. Two dimensional echocardiograms (**left**) and an artist's reconstructions (**right**). **Upper panel,** longitudinal scan of the left ventricle demonstrating a huge left atrium (LA) prolapsing behind the left ventricle (LV). **Lower panel,** transverse cross-sectional scan of the left ventricle visualizing the posteriorly located left atrial prolapse. AR = aortic root; MV = mitral valve (rheumatic); VS = ventricular septum.

counting for both the posterior echo-free space behind the left ventricle in the M mode examination and the left ventricular cineangiographic findings. The patient subsequently underwent mitral valve replacement with a porcine heterograft. At operation a huge left atrium was found that prolapsed behind the left ventricular posterior wall. In addition, no pericardial effusion and no ventricular septal defect or false aneurysm of the left ventricle was present. After a stormy postoperative course, the patient recovered sufficiently to allow a second two dimensional echocardiographic examination. The results were similar to the preoperative findings except for the presence of a prosthetic mitral valve (Fig. 4).

Case 2: A 68 year old woman with a history of congestive heart failure was admitted to this center for evaluation, which revealed the presence of mitral stenosis and insufficiency. An M mode echocardiogram disclosed rheumatic mitral valve disease and left atrial enlargement. There was an echo-free space behind the left ventricular posterior wall, suggesting the presence of a posterior pericardial effusion. A two dimensional echocardiogram revealed a huge left atrial cavity that prolapsed behind the left ventricle (Fig. 5). Cardiac catheterization indicated critical mitral stenosis with mild mitral regurgitation. The lateral projection of a biplane left ventricular cineangiogram revealed a huge left atrium that prolapsed behind the left ventricle (Fig. 6). Mitral valve replacement was performed, and at operation a huge left atrium with an intracavitary clot was noted. No excessive pericardial fluid was present.

Case 3: A 62 year old woman was referred for cardiac evaluation, which revealed the presence of mitral stenosis and insufficiency. An M mode echocardiogram revealed rheumatic mitral valve disease, left atrial enlargement and the presence of an isolated echo-free space behind the left ventricular posterior wall, suggesting pericardial effusion. A right anterior oblique cineangiogram demonstrated a huge left atrium that prolapsed behind the left ventricle. Mitral valve replacement was performed, and at operation a huge left atrium was noted. However, approximately 500 cc of pericardial fluid was also found and removed.

In the immediate postoperative period a two dimensional transverse cross-sectional echocardiogram of the left ventricle again demonstrated a large echo-free space behind the left

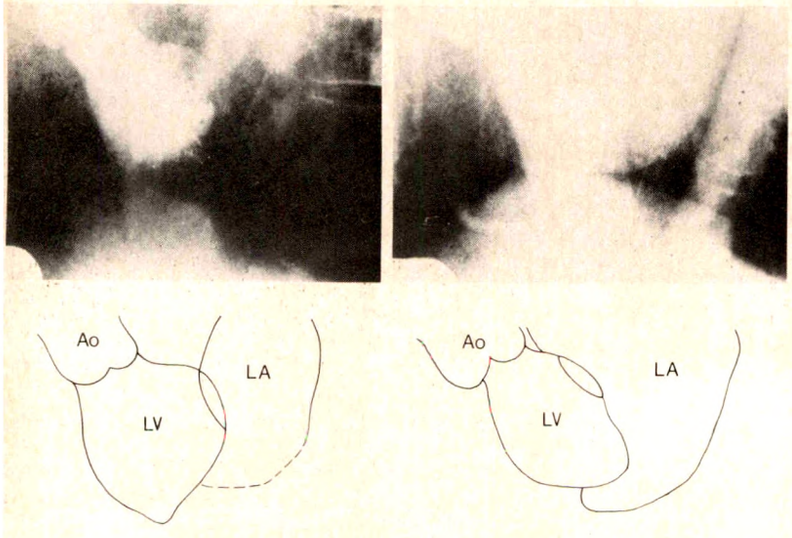

FIGURE 6. Case 2. **Top,** two representative frames from the lateral projection of the left ventricular cineangiogram, with an early contrast injection phase on the **left** and a late injection phase on the **right. Bottom,** an artist's reconstruction of the frames. The late phase frame on the **right** shows complete filling of the left atrium (LA) with prolapse of the enlarged chamber behind the left ventricle (LV).

ventricle, similar to that noted on the preoperative examination. The injection of 2 cc of indocyanine green dye through an indwelling left atrial catheter confirmed that the echo-free space was due to left atrial prolapse (Fig. 7).

Discussion

Limitations of M mode echocardiography: Echocardiography is an excellent technique for detecting abnormal accumulations of pericardial fluid.[5–8] M mode echocardiographic tracings of good technical quality have detected fluid accumulations as small as 15 cc.[13] However, improper echocardiographic control settings can obscure the diagnosis of much larger amounts of pericardial fluid.[7] In addition to false negative examinations, the narrow field of view of M mode echocardiography has led to false positive diagnoses of posterior pericardial effusion in the presence of left pleural effusion and also in mitral anulus calcification.[7] Extreme medial transducer augulation has been thought to produce an echo-free space behind the left ventricular posterior wall due to inclusion of an enlarged coronary sinus or one of the pulmonary veins in the ultrasonic beam.[7] The descending aorta was recently shown to create an isolated echo-free space behind the left ventricle.[11]

M mode echocardiography has proved reliable in the detection of left atrial enlargement.[1–4] However, because of its one dimensional character, the technique may produce erroneous estimates of left atrial size in the presence of asymmetric left atrial enlargement.[9,10] Indeed, measurement of the left atrium in two dimensions, one from the suprasternal area and one from standard precordial approach, has been reported to detect nonspherical left atrial shapes.[14] One case of the false positive diagnosis of pericardial effusion by M mode echocardiography in the presence of a huge left atrium was previously reported.[15] We have described three additional cases in which this diagnosis was confirmed by two dimensional echocardiography.

Role of two dimensional echocardiography: A large left atrium is frequently a result of mitral valve disease. An enlarged atrium does not commonly project behind the left ventricular posterior wall but, when present, it can mimic a posterior pericardial effusion on M mode examination. In our three cases the spatial orientation provided by two dimensional echocardiography permitted accurate recognition of portions of a hugely dilated left atrium that prolapsed behind the left ventricular posterior wall and resulted in the M mode findings.

In Case 1 with mitral insufficiency, a right anterior oblique left ventricular cineangiogram demonstrated contrast medium beyond the contours of the heart behind the left ventricle. This unexpected finding suggested the presence of a ventricular septal defect or false aneurysm of the left ventricle.[13,16] The two dimensional echocardiogram showed a huge left atrium that extended behind the left ventricle. The incompetent mitral valve allowed left atrial filling after the injection of dye into the left ventricle, which resulted in this unusual cineangiogram. In Case 2 with mitral insufficiency a right anterior oblique cineangiogram correctly identified left atrial prolapse. In Case 3 with mitral insufficiency the lateral projection of a biplane left ventricular cineangiogram easily visualized the prolapsed portion of a huge left atrium.

We conclude that two dimensional echocardiography should be utilized in the presence of a large left atrium to look for left atrial prolapse when isolated echo-free spaces are noted behind the left ventricular posterior wall on M mode echocardiography. Also, left atrial prolapse may result in left ventricular angiographic findings suggesting a ventricular septal defect or a false aneurysm of the left ventricle in the single plane right anterior oblique projection.

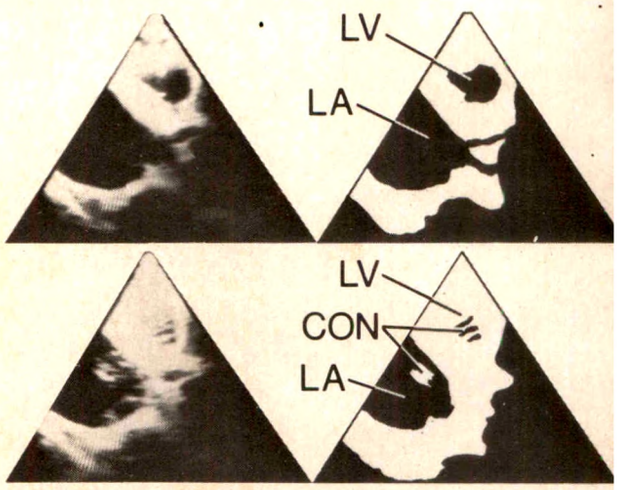

FIGURE 7. Case 3. Two dimensional echocardiographic transvers sections through the left ventricle (**left**) and an artist's reconstruction (**right**). The **upper panel** reveals a huge echo-free space posterior t the left ventricle (LV). The **lower panel** is the same view after injectio of indocyanine green dye directly into the left atrium. It reveals echo cardiographic contrast solution (CON) within the prolapsed left atriur (LA) and the left ventricle.

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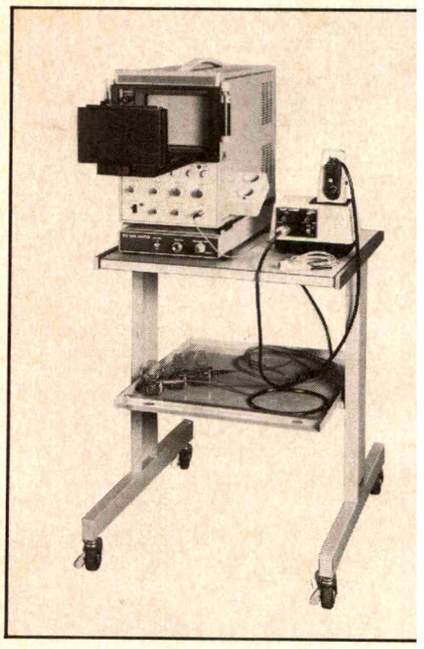

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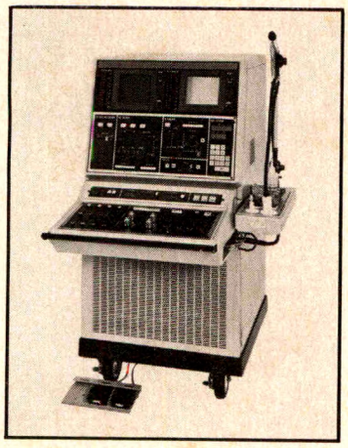

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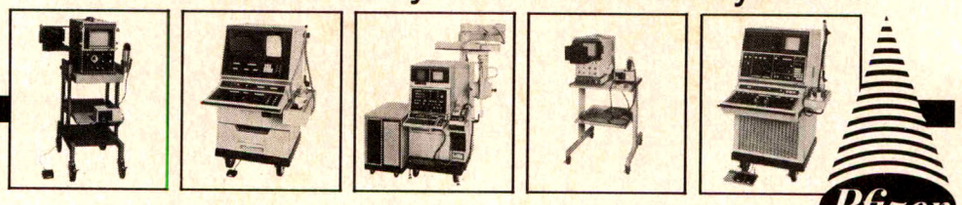

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Preface

The focus of this Bethesda Conference on the Prevention of Coronary Heart Disease was the role of physicians. From its inception, this orientation was explicitly defined by the convenor and the co-sponsors—the American College of Cardiology, the American Heart Association, the National Heart, Lung, and Blood Institute and the Center for Disease Control. The concept was that physicians had already contributed much to the coronary heart disease prevention effort and have the potential to do much more; therefore, more attention should be given to realizing their full potential, especially in concert with allied health professionals.

Correspondingly, it was agreed that the main concern of this Conference was *not* the role of voluntary or official agencies or of lay organizations and groups in the community—as important as is their contribution. Further, it was also agreed that this Conference was not to undertake a systematic review once again of the data base and scientific foundation of the effort to prevent coronary heart disease, for example, in regard to modifiable lifestyles (eating, drinking, smoking, exercise patterns) and other risk factors; this had been done repeatedly by competent and representative groups o experts in the 1970s—for example, for the Americar Heart Association, the Inter-Society Commission fo Heart Disease Resources, the National Heart, Lung, and Blood Institute and other official agencies—includin reports issued this year and last. The recommendation of these groups were accepted as scientific foundation for the Conference, that is, reasonable and sound bes judgment consensus assessments of currently extan knowledge and its practical implications, with the rec ognition that varying emphases and dissenting view existed, that relevant research was ongoing, that mor research was needed and that with further informatio and experience preventive approaches would evolve an advance. In this context, there was also the clear rec ognition that physicians could and should contribut much more to the coronary prevention effort now an in the years immediately ahead. The Conference aime to achieve a consensus—in the tradition and spirit o Bethesda Conferences—to this end.

THE STEERING COMMITTE

* The recommendations set forth in this report are those of the Conference participants and do not necessarily reflect the official position of the American College of Cardiology. This study was supported in part by NIH contract 263-80-C-0510 from the National Institutes of Health of the Department of Health and Human Services.

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Opening Statement

JEREMIAH STAMLER, MD, FACC

On behalf of the American College of Cardiology, the initiator of this Bethesda Conference, and its co-sponsors—the American Heart Association, the National Heart, Lung, and Blood Institute and the Center for Disease Control—it is a great honor and pleasure for me to open this Bethesda Conference on the Prevention of Coronary Heart Disease. As you all know, in the decade of the 1970s substantial progress was registered in controlling the epidemic of premature coronary heart disease in the United States. Our mortality rates declined more than 25 percent. We set the pace for other countries in this regard. However, our rates of sickness, disability and death from this modern plague still remain high, among the highest in the world. Hence this Conference.

The focus of this Conference is the role of the physician in the effort to make substantial further advances in the prevention of coronary heart disease. Clearly, physicians have already contributed significantly Witness the millions of people with high blood pressur whose condition has been detected, evaluated, treate and brought under long-term control. Witness th millions who on the advice of their physicians hav changed their eating habits to control hyperlipidemia obesity, hypertension, diabetes mellitus—the majo coronary risk factors. While our profession has alread done much, clearly there is a great deal remaining to b done. In the tradition of the Bethesda Conferences, w are here to arrive at a consensus as to the most effectiv ways to go forward with this effort in the 1980s. For thi purpose, it is excellent that we have here today repre sentatives of the key medical and health professiona organizations whose members must do the job. All of u are particularly gratified with your response to our in vitation and we especially extend a warm welcome to a of you.

The Mission of Prevention

ROBERT O. BRANDENBURG, MD, FACC

On behalf of the American College of Cardiology, and its co-sponsors, the American Heart Association, the Center for Disease Control, and the National Heart, Lung, and Blood Institute, we are very pleased that you are here. We are delighted that we can serve as the site for this important conference.

Four years ago, the Long Range Planning Committee of the American College of Cardiology spent many hours developing a mission statement. I'd like to review it with you.

The mission of the College is to ensure optimal care for persons with cardiovascular disease or the potential fc developing it; and ultimately, through appropriate educa tional and socioeconomic activities, to contribute signifi cantly to the prevention of cardiovascular disease.

It is difficult to imagine a Conference more appro priate to this mission than the one about to begin. As clinician I recognize that preventive cardiology pro grams are difficult to execute. It is my hope and ex pectation that, as a result of this Conference, the prac tice of preventive coronary artery disease programs wi be expedited and advanced.

The Opportunity and the Task

THOMAS N. JAMES, MD, FACC

No one—certainly no one here—is likely to speak against the value of preventing disease. The American Heart Association is fully committed to doing everything possible to prevent heart disease, and we share with many others a great pride in seeing what has been done in preventing rheumatic heart disease. At this meeting, Dr. Stamler will lead and stimulate wide-ranging discussions on what physicians can do to prevent coronary heart disease. Because this subject is so important and timely, and because the participants were invited on the basis of their considerable professional stature, one may predict that your report will be widely read and influential. As you deliberate these two days, would you please keep in mind these few points:

1. While death from coronary disease has steadily decreased for more than 10 years, no one knows whether the incidence and severity of coronary disease in this period have increased, decreased or stayed the same.
2. About 9 of 10 patients with hypertension, a major risk factor for coronary disease, have essential hypertension, the cause of which is unknown.
3. Prevention and reduced risk are not the same thing. Be careful to distinguish between them because your credibility of statement is at stake.
4. As a physican you advise patients one at a time. And data from large population studies may or may not apply to the individual person. Remember the individual.

You have a remarkable opportunity, and I'm confident that you are up to the task. I wish you every success in your work.

The Physician and Prevention

ROBERT I. LEVY, MD, FACC

The National Heart, Lung, and Blood Institute and the Center for Disease Control are delighted to be the federal sponsors for this program. Disease prevention and health promotion are major and growing concerns of the Center for Disease Control. Today, representing the Center with us is Mr. Horace Ogden, director of the Center's Bureau of Health Education.

The commitment of the National Heart, Lung, and Blood Institute to prevention is long-standing. That is the ultimate aim, the ultimate objective of all our work in all the diseases we face; it is clearly mandated in our legislation. And as I am sure you have all heard me say again and again, we think of prevention throughout the biomedical research spectrum.

We think of our aim of prevention when we talk about knowledge acquisition; more work that has to be done, as Dr. James has indicated, in etiology, pathophysiology. We think of prevention as an objective in our knowledge validation activities, certainly our multicenter clinical trials that are underway now, testing the risk factor hypothesis. And we think of prevention in our many areas in knowledge translation and knowledge dissemination to the community.

Dr. Stamler has already spoken of, and the next speakers will clearly talk about, the importance and potential of coronary disease prevention. Coronary artery disease is the major killer disease today. It is coming under control, if we look at mortality figures, but it still is responsible for more than twice as many deaths as any other disease.

Coronary artery disease is caused predominantly by a silent process we call atherosclerosis, a process that all too frequently manifests as its first sign sudden death—a flag to all of us that prevention has to be our goal. To wait to palliate clearly would be to wait too long.

Dr. Stamler has already mentioned that 2 years ago we had a conference to examine the cause or nature of the decline in cardiovascular disease. It was quite clear from the facts at hand at that conference that the decline was real. However, as Dr. James suggests, we could not agree on the cause of the decline. We could not quantitatively agree how much had come because of the changes in lifestyle and habits, in smoking and blood pressure and nutrition and exercise that the public had undertaken in the last decade; and how much we could attribute to improved medical care and better treatment. But I think what did come out of that conference

was a consensus that prevention had played a role, and a consensus that preventive activities should and must be intensified in the future.

If I had any doubt about the role of the physician in prevention, that doubt has completely disappeared as I have witnessed the success of the National High Blood Pressure Education Program in which physicians have taken the lead from the first. Surveys continue to show us that the public feels strongly that medical advice about changes in lifestyle habits would be most positively responded to if it came from their physicians. We also learned from the public that they feel that less than half of their physicans spend any considerable time providing them with information dealing with prevention. If I had to give a challenge to this conference, I would list four charges: (1) This conference needs to promote the concept that prevention is an integral and beneficial part of the practice of medicine. (2) It needs to identify areas in which the physican can make significant contributions. (3) It needs to provide examples or guidance to the physician in various settings. And finally (4) it needs to motivate those who are not now actively engaged and to reinvigorate and reinforce those who are.

There have been examples of successful programs in which government has disseminated information to physicians. Some of these have resulted in improved health care. However, when it comes to advising physicians on how to practice, I don't have to say that government involvement is usually not appreciated.

Therefore, it is important that this Conference, and the messages that it will develop, is the product of practicing physicians talking to physicians. It is gratifying to me that this conference is the brainchild of the American College of Cardiology, and that the bulk of the organizations participating are physician-oriented. More than gratification: it gives me great optimism that the lessons we learn during these next 2 days won't be left in Bethesda, but will reach those who can and should put them into practice.

The Concept of Bethesda Conferences

WALTER H. ABELMANN, MD, FACC

On behalf of the Bethesda Conference Committee of the American College of Cardiology, I thank you for participating in this Conference. Allow me to say a few words about the concept of Bethesda Conferences and about their methodology. The College recognizes that there are important topics and areas of concern to the profession it represents on which there is no general agreement. Yet, in many of these areas, a position and often action on the part of the physician and society are mandated and guidance is needed.

The Bethesda Conferences are designed to step into this difficult zone, by providing recommendations based on the consensus of a broadly representative sample of experts. The method we use to do this is the so-called Delphi method. The Delphi method was developed over 25 years ago at the Rand Corporation as a method of arriving at consensus about long-range forecasting as an aid to planning. This method underlies the Bethesda Conferences, introduced by the College in 1966. In its traditional form, the method consists of sending a questionnaire to a group of experts and then making a synthesis for further consideration. This process may be repeated as necessary. The strength of this method of predicting future developments lies in the selection of a broad sample of experts and the provision of opportunities for anonymous expression of views as well as for interchange of views and ideas.

Thus, each one of you is here as an expert on some aspect of our topic, and your individual contribution is essential to the validity of the process. If the topic of our deliberation were not in some flux and beset with uncertainty, we would not have assembled for this Conference. Therefore, the consensus document that we hope will result, while representing the best guidance we can give at this time, is not meant to stand up in its entirety in the face of future research and discoveries. What should stand up for some time to come is the physician's approach to his or her responsibility toward the patients and the population he or she serves with regard to preventive cardiology, that is, the manner in which he or she can and should discharge this responsibility.

I would like to charge this Conference, then, with the task to focus upon this aspect of the problem, irrespective of such disagreement as may arise over the relative strength and importance of given risk factors for coronary heart disease. Whereas the conclusions and recommendations of this Conference will stand on their own and do not represent a formal position of the American College of Cardiology, the College does accept responsibility for conducting this consensus conference in the tradition of excellence set by past Bethesda Conferences.

The Scientific Foundation for Prevention of Coronary Heart Disease

THEODORE COOPER, MD, FACC

We are in an age of preoccupation with numbers—so-called data. Ideas that cannot be quantified have little or no acceptance. Truth is revealed by a statistical formula, even though the science of biostatistics is acknowledged to be evolving. We are still trying to fit poorly understood distributions into mathematical concepts based on understood distributions. It is therefore important, to recognize the factors that influence appreciation or evaluation of studies. An acute illness presents relatively little problem compared with a chronic illness such as coronary heart disease. Yet, we seem committed to the view that the numbers are the way to paradise.

For the public official, for the advisors to the public official, for the consumer activist, for the medical liability lawyer, paradise is having what is called a "definitive study" on whether eating fewer eggs will prevent coronary heart disease. For the practicing physician, definitive studies are also of help, if he or she could accept what is meant by definitive. I would guess that the most distressing thing about studies today, for the practicing doctor, is to try to interpret studies that claim a 20 to 25 percent difference between control and treated groups, statistically significant to a given power like 0.001. Does that mean that only some will benefit? Or something else?

Some of you might scoff at such a question. However, such issues are at the heart of physician acceptance of statistical studies. I have often been asked why seemingly competent physicians would adopt suspect practices and not accept the revealed truth of certain studies, particularly government-sponsored studies, which most of them are. And I have often been told by practitioners that the problem with the studies is that the people who did them, particularly the people who designed them, don't know the first thing about patients or disease management.

Recent Decline in Coronary Mortality

I mention these points because it was my assignment to review the scientific foundations of the preventive approach to management of coronary heart disease. I have reviewed—as you have—a wide variety of documents and data from epidemiologic studies and clinical trials on various factors believed operative in the pathogenesis of the disease. It is particularly pleasing to be able to say that total mortality has been declining, not just mortality due to heart disease or strokes. In fact, if one were not discriminating one might caution about pushing programs too hard; it doesn't seem too far to zero. But discriminating we must be; it is perfectly clear that there is still a formidable job to be done and, despite truly impressive gains over the past several years, we must press on.

In order to present proposals that are designed for further reduction in mortality, we should probably understand, and perhaps agree on, what the basis of the recent improvement is or was. It seems that study of the same data made available to you and me left the experts somewhat confused or at least with different viewpoints. However, I was reassured to learn that they thought the decline was real. Results have been presented in various publications and forums supporting the view that modifying "the risk factors" has had something to do with the trends. The consensus is quite strong that cigarette smoking is a thing to avoid if you don't smoke—or to stop if you do. But there are other factors on which the agreement is not so clear from epidemiology and clinical trials on various factors believed operative in the pathogenesis of the disease.

The Role of Risk Factors

There are some studies not included in your program packets that bear importantly on our task. These studies address the question of where people get their information about health and medical care and what they believe. On many occasions, when urging physicians to "*do more prevention,*" they point out that "everybody knows these things are not settled." The scientific foundation for this kind of approach must include a variety of other approaches of inquiry. An important set of studies that asks people where they get their information, and what they think is reliable and what they think is not reliable, is extremely important. For example, the recent discussions about cholesterol and the American diet that resulted from the release of a report from the National Academy of Sciences left some people, including some doctors, confused and annoyed. I mention this here not to open wounds or to join the debate but only to indicate the importance of an important observation. What do people think is a reliable source of useful medical and health information? Their doctor—of course! Not the government.

When I was a public official and I would speak to lay audiences about good health practices and make an assertion backed up by a panel of experts who had evaluated complex studies, the people would go to their own doctors and ask, "Is that right?" I am somewhat

reticent to present to this audience the data from Framingham or the Diet Heart Study, or the various Veterans Administration studies on diet or hypertension, or the Hypertension Detection and Followup Program or the studies of Dr. Stamler and his group and so on. You probably know them better than I. So I shall not present the specific data. I shall comment on the foundation these studies offer. I believe they mean something. I believe they indicate that attention to the risk factors should have an influence on the development of the disease. I do not believe that it is the entire answer to prevention. But in the current state of the art it forms a basis for some specific approaches that should be utilized by practitioners. Furthermore, I am confident that changes will occur, for in fact, as you will hear in the next presentation, change has occurred.

It is appropriate to ask if the scientific foundation is adequate. Having said I believe that the studies are meaningful, I might be expected to say that they are adequate. The foundation is an adequate basis for action, but certainly not adequate to reach a decision that no further studies are needed. More studies—lots more—are required. But we can take action on less than complete or perfect information. There are several reasons to support this position. First, there are data to support the view that in some persons weight control, dietary management, a rational program of physical activity, lowering elevated blood pressures, controlling diabetes, cessation of cigarette smoking and avoiding excessive alcohol consumption will improve the chances of avoiding clinical coronary heart disease. Second, we know that virtually all of these measures have little or no serious risk of harm to the person—when properly instituted. Third, the cost of the required modifications of this life style or therapeutic interventions is modest. Fourth, the technical demands of the program for the physician, other health professionals or people themselves are relatively simple. So my point then is that the programs that require change in what people do and often enjoy doing—changes that can run contrary to well ingrained social and economic aspirations—will have to have the imprimatur of the personal health guru, the doctor.

I am delighted to see the acceptance of the need to pay attention to the young. Studying the young has special problems. Some of the problems are cultural and ethical. But the greatest deficit is that there are too few studies. However, the interests of investigators are changing and the notion is gaining credibility that chronic cardiovascular disease may begin early in life. And this is a most important fact to accept in the design of a program of prevention.

I am also pleased to note that genuine studies support the notion that prevention can be effectively practiced at the work site. I have resisted talking about high blood pressure as the end-all and be-all of the field. However, the recent approach to preventive education and control in this facet of the problem of coronary heart disease has been rewarding indeed. High blood pressure programs have provided excellent demonstrations that prove preventive approaches will work. It has been particularly gratifying to me to see the plethora of good results from the studies and control programs alike, although the experts are not unanimous in their approach and analysis of the data. The Hypertension Detection and Followup Program must be looked upon as an enormous contribution of great importance to the field.

Long-term clinical studies are difficult and expensive to carry out. We are learning how difficult it is to design studies that can ensure success. We are not even certain that we know what a so-called negative result means—much less what a mixed or marginal answer means. Lifestyles and habits are changing and practices are changing; hence, reference points are changing. Therefore, with the best of intentions and thoroughness of design, our current technology will often fall short of answering the question, and we must be wary of concluding that a big indecisive study means that it doesn't work. So I again call for common sense as well as for more data in reaching judgments about what to recommend for maintaining well-being.

Behavioral and Social Factors

Finally, one area of risk factors is receiving too little attention. Indeed, some might feel that these factors should not be classified as risk factors. I refer to behavioral and social factors. I believe that studies in this area are important for two principal reasons. First, they offer possibilities—both direct and indirect—of understanding pathologic mechanisms of coronary heart disease and its expression. Second, they are relevant to patient adherence to programs or what is usually called compliance.

Here is an area that is particularly important for constructing an action program for physicians. Both patient and physician become discouraged in seeing no results. We are a "fast result" society. What we are asking people to do is to look beyond the usual short term, to generation-long and lifelong practice modification.

There is a tendency to group all or most of the things directly related to prevention of coronary heart disease as elements of lifestyle—such activities as eating, smoking, drinking, working, playing, and so on. In a very real sense we are asking people to change many of the things they do that have been familiar cultural, social and religious practices. Eating is a prime example. We could very easily fall prey to the notion that the purpose of eating is nutrition only. As you well know, it is much more than that. There is indeed much more to life than just living. So we must guard against predicting disaster from the pulpit, and we must try not to legislate lifestyle out of frustration with the rate of progress we have seen.

We must educate not only patients, but also physicians and society as a whole. We look toward this Bethesda Conference to produce a program of specific steps to follow to prevent disease.

Primary Prevention of Coronary Heart Disease: The Last 20 Years

JEREMIAH STAMLER, MD, FACC

My assignment is to review developments and experiences over the last 20 years in the effort to achieve the primary prevention of coronary heart disease in the United States. First, I will briefly review the development of policy for the health professions and the general public. Then I will describe the changes that have taken place in lifestyles and lifestyle-related risk factors in our population. Finally, I will present data on the decline in mortality from coronary heart disease over the last decade.

Development of Public Policy

To the best of my knowledge, the initial call for an effort to prevent coronary disease was the "*Statement on Arteriosclerosis, Main Cause of 'Heart Attacks' and 'Strokes,'* " co-authored in 1959 by Paul Dudley White, Louis N. Katz, Samuel Levine, Irvine H. Page, Howard B. Sprague, Frederick J. Stare, Irving S. Wright and myself.[1] This was an initiative of a group of individuals, cardiologists and cardiovascular researchers, not of an organization, voluntary or official. This brochure was circulated in hundreds of thousands of copies by the National Health Education Committee, with the support of Mrs. Mary Lasker, whose name looms large in regard to progress in cardiovascular research and control. This document, written almost a quarter of a century ago, called attention to all of the traits—hypercholesterolemia, cigarette smoking, hypertension—later designated major risk factors, plus overweight and a positive family history of premature hypertensive and atherosclerotic disease.

A year later, in 1960, the American Heart Association issued its first statement on cigarette smoking and cardiovascular disease.[2] The committee drafting that report was chaired by my mentor and chief, Dr. Louis N. Katz, also a co-author of the just cited *Statement*. He and Paul Dudley White, Samuel Levine, Irvine Page, Howard Sprague, Irving Wright—leaders among the older generation of cardiologists and cardiovascular investigators—were statesmen. They all were deeply concerned to assure that the fruits of research were made available as rapidly and effectively as possible to the profession and the public.

In 1961, the American Heart Association issued its first statement on diet and coronary heart disease,[3] calling attention both to the matter of lipid composition of the diet—avoidance and correction of high intake of saturated fat and cholesterol—and of calorie imbalance and consequent obesity. As you all know, the American Heart Association has at intervals updated these documents.[4–7]

In 1964, the landmark *Report of the Advisory Committee to the Surgeon General on Smoking and Health* was published,[8] probably with the first clear lead from the federal government relating to the effort to prevent coronary heart disease.

In 1970, the Inter-Society Commission for Heart Disease Resources issued its *Report on the Primary Prevention of the Atherosclerotic Diseases*.[9] It, like its predecessors, was thoroughly documented with references to research studies delineating the scientific foundation of the prevention effort. Figure 1 presents the succinct summary the Inter-Society Commission distilled of its recommendations: first and foremost, the need for a strategic emphasis on primary prevention as long-term national policy; then the effective implementation of that strategy, in order to accomplish changes in diet to prevent or control hyperlipidemia, obesity, hypertension and diabetes; the elimination of cigarette smoking; and the pharmacologic control of elevated blood pressure where indicated. After that summary of its approach, the *Report* gave detailed recommendations on implementation. The Inter-Society Commission—established as a result of federal legislation and at the request of the Assistant Secretary for Health (the Surgeon General)—was made up of representatives of all the key medical and health professional organizations concerned with this challenge, including those represented here today.

In the next year, 1971, both the White House Conference on Nutrition and the Task Force on Arteriosclerosis of the National Heart and Lung Institute also addressed these matters and made available to the health professions and the public similar summary recommendations, in agreement with those already noted.[10,11]

In 1973 there was another important development: the official assumption of federal responsibility, at the Cabinet level, for control of a major unsolved mass public health problem, high blood pressure—with the launching by the Secretary of Health, Education, and Welfare of the National High Blood Pressure Education Program, under the aegis of the National Heart, Lung, and Blood Institute.[12]

RECOMMENDATIONS FOR PRIMARY PREVENTION
OF THE ATHEROSCLEROTIC DISEASES
INTER-SOCIETY COMMISSION FOR HEART DISEASE RESOURCES, 1970

"The Commission recommends that a strategy of primary prevention of premature atherosclerotic diseases be adopted as long-term national policy for the United States and to implement this strategy that adequate resources of money and manpower be committed to accomplish:

"Changes in diet to prevent or control hyperlipidemia, obesity, hypertension and diabetes.

"Elimination of cigarette smoking.

"Pharmacologic control of elevated blood pressure."

FIGURE 1. Recommendations for primary prevention of the atherosclerotic diseases. Inter-Society Commission for Heart Disease Resources, 1970.

In the late 1970s the Select Committee on Nutrition and Human Needs of the U.S. Senate presented a set of dietary goals for the United States, emphasizing improvement in both the lipid and carbohydrate composition of the diet (Fig. 2).[13] That report also called attention to the matter of avoiding and correcting calorie imbalance and consequent obesity and high sodium intake. It also succinctly indicated reasonable approaches to food selection to achieve these dietary goals (Fig. 3). Like all such recommendations, these were also concerned to aid Americans in maintaining and even improving intake of all essential nutrients.

Implicitly or explicitly, they are also dedicated to helping Americans to continue—in a healthier way—to enjoy one of life's pleasures, the pleasure of eating, for example, by taking tips from Mediterranean and Far Eastern eating styles. In the course of this effort, the American Heart Association produced a national best seller, the *American Heart Association Cook Book*, now in its third edition.[14]

In 1979, the American Diabetes Association updated its earlier reports, presented jointly with the American Dietetic Association, on principles of nutrition and dietary recommendations for individuals with diabetes.[15–17]

At the turn of the decade, the Report of the Surgeon General, *Healthy People—A Report on Health Promotion and Disease Prevention*,[18] dealt comprehensively with the major present-day challenges to the health of the American people at each stage of life, including those of better lifestyles from childhood on—better habits in regard to eating, drinking, smoking and exercise—to help control the epidemic of coronary heart disease, and other major chronic disease problems as well. The Institute of Medicine of the National Academy of Sciences contributed importantly in the devel-

DIETARY GOALS FOR THE UNITED STATES

1. TO AVOID OVERWEIGHT, CONSUME ONLY AS MUCH ENERGY (CALORIES) AS IS EXPENDED; IF OVERWEIGHT, DECREASE ENERGY INTAKE AND INCREASE ENERGY EXPENDITURE.
2. INCREASE THE CONSUMPTION OF COMPLEX CARBOHYDRATES AND "NATURALLY OCCURRING" SUGARS FROM ABOUT 28 PER CENT OF ENERGY INTAKE TO ABOUT 48 PER CENT OF ENERGY INTAKE.
3. REDUCE THE CONSUMPTION OF REFINED AND PROCESSED SUGARS BY ABOUT 45 PER CENT TO ACCOUNT FOR ABOUT 10 PER CENT OF TOTAL ENERGY INTAKE.
4. REDUCE OVERALL FAT CONSUMPTION FROM APPROXIMATELY 40 PER CENT TO ABOUT 30 PER CENT OF ENERGY INTAKE.
5. REDUCE SATURATED FAT CONSUMPTION TO ACCOUNT FOR ABOUT 10 PER CENT OF TOTAL ENERGY INTAKE; AND BALANCE THAT WITH POLY–UNSATURATED AND MONO–UNSATURATED FATS, WHICH SHOULD ACCOUNT FOR ABOUT 10 PER CENT OF ENERGY INTAKE EACH.
6. REDUCE CHOLESTEROL CONSUMPTION TO ABOUT 300mg. A DAY.
7. LIMIT THE INTAKE OF SODIUM BY REDUCING THE INTAKE OF SALT TO ABOUT 5 GRAMS A DAY.

FIGURE 2. Dietary goals for the United States. Select Committee on Nutrition and Human Needs of the U.S. Senate.

CHANGES IN FOOD SELECTION AND PREPARATION
TO ACHIEVE THE U.S. DIETARY GOALS

1. INCREASE CONSUMPTION OF FRUITS AND VEGETABLES AND WHOLE GRAINS.
2. DECREASE CONSUMPTION OF REFINED AND OTHER PROCESSED SUGARS AND FOODS HIGH IN SUCH SUGARS.
3. DECREASE CONSUMPTION OF FOODS HIGH IN TOTAL FAT, AND PARTIALLY REPLACE SATURATED FATS, WHETHER OBTAINED FROM ANIMAL OR VEGETABLE SOURCES, WITH POLY–UNSATURATED FATS.
4. DECREASE CONSUMPTION OF ANIMAL FAT, AND CHOOSE MEATS, POULTRY AND FISH WHICH WILL REDUCE SATURATED FAT INTAKE.
5. EXCEPT FOR YOUNG CHILDREN, SUBSTITUTE LOW–FAT AND NON–FAT MILK FOR WHOLE MILK, AND LOW–FAT DAIRY PRODUCTS FOR HIGH FAT DAIRY PRODUCTS.
6. DECREASE CONSUMPTION OF BUTTERFAT, EGGS AND OTHER HIGH CHOLESTEROL SOURCES. SOME CONSIDERATION SHOULD BE GIVEN TO EASING THE CHOLESTEROL GOAL FOR PRE–MENOPAUSAL WOMEN, YOUNG CHILDREN AND THE ELDERLY IN ORDER TO OBTAIN THE NUTRITIONAL BENEFITS OF EGGS IN THE DIET.
7. DECREASE CONSUMPTION OF SALT AND FOODS HIGH IN SALT CONTENT.

FIGURE 3. Recommended changes in food selection and preparation to achieve the U.S. dietary goals. Select Committee on Nutrition and Human Needs of the U.S. Senate.

. opment of this report.[19] Early this year, the U.S. Department of Agriculture and the U.S. Department of Health, Education and Welfare (now Health and Human Services) published the colorful folder, *Nutrition and Your Health: Dietary Guidelines for Americans.*[20]

Early this year also, the Committee on Dietary Allowances, Food and Nutrition Board, National Academy of Sciences, in the ninth edition of its *Recommended Dietary Allowances,*[21] presented guidelines on desirable amounts and proportions of dietary fat and carbohydrate: not more than 35 percent of calories from total fat, particularly in diets below 2,000 calories; greater reduction in fats containing predominantly saturated fatty acids, such as those from animal sources, than in vegetable fats containing unsaturated fatty acids; an upper limit of 10 percent of dietary energy as polyunsaturated fatty acids; reduced intake of refined sugars; maintenance or even increase in complex carbohydrate; for many individuals a reduction in alcohol consumption. The comment was made, "These recommendations for desirable types and amounts of dietary fat and carbohydrate do not entail radical changes in eating habits and could be accomplished with the United States food supply. Indeed many individuals normally have dietary practices that follow this pattern. The American Heart Association and the Working Party of the Royal College of Physicians of London believe that these dietary recommendations, in conjunction with measures to decrease other risk factors, have a reasonable hope of being beneficial." [21] A few months later, another Food and Nutrition Board report[22]—while advising dietary measures to control obesity (including lower intake of fats, oils, sugars and alcohol) and moderation in salt intake—made no recommendations about ingestion of saturated fats, and ". . . no specific recommendations about dietary cholesterol for the healthy person." [22] This statement, given wide publicity, led to extensive discussion and debate in the general press and before Congress, since it was rightly regarded as at variance on the matter of dietary lipids with conclusions and recommendations of expert committees over the last two decades. A detailed scientific critique of this report is available.[23]

Subsequently, the American Heart Association completed its report on *Nutrition Education of the Young,* and its updated general statement on *Risk Factors and Coronary Disease.*[24,25] The first of these reaches to a key issue and a central concern of this Conference: *primary* habit formation and the development of healthy lifestyles from early childhood on. The second serves as a key contemporary statement of the scientific foundations of this Conference.

Clearly, while there are dissenting views,[22,26] we have effective consistent public policy leads, developed by expert groups and responsible organizations over 2 decades, reflecting a rich mine of research information and a broad consensus in the scientific, professional, voluntary and official communities. And, in fact, similar position statements are available from expert groups in other countries experiencing the epidemic of coronary heart disease, and from the World Health Organization and the International Society and Federation of Cardiology (both represented here).[27–36]

May I add finally that we can be proud—in a healthy, nonchauvinistic way—that we in the United States have generally given the lead and set the pace in the development of public policy on the primary prevention of coronary heart disease.

TABLE I

Trends of Food Products Available for per Capita Annual Consumption, U.S.A., 1950–1978

Product	1950	1960	1970	1974	1978	% Change 1950 → 1978
Eggs (n)	389	335	311	288	273	−29.8
Milk fat solids*	29	25	21	20	20	−31.0
Nonfat milk solids*	44	43	41	38	39	−11.4
Fats and oils, total*,†	46	45	53	53	56	+21.7
Butter	11	7	5	5	5	−54.5
Lard	13	8	5	3	2	−84.6
Margarine	6	9	11	11	12	+100.0
Shortening	11	13	17	17	19	+72.7
Other	9	11	18	20	22	+144.4
Meats*	145	161	186	191	187	+29.0
Beef	63	85	114	117	120	+90.5
Pork	69	65	66	69	62	−10.1
Chicken and turkey*	25	34	50	50	58	+132.0
Fish*	12	10	12	12	13	+8.3

*lb/person per year. † Total is by fat content, individual items are by actual weight.

Changes in Lifestyle and Related Risk Factors

The development of public policy has been steady and progressive over these 20 to 25 years. But the resources for dissemination have been modest. What about the American people? Have they "heard the message" and acted on it?

Eating patterns: Intriguing data are available from a 1976 U.S. Department of Agriculture survey.[37] It dealt with whether Americans have recently changed their eating styles because of health concerns. About half of a random sample of the population replied in the affirmative, indicating they had done so either to alleviate existing health problems or to avoid potential ones. Some stated they had done so on advice of their physicians, others on their own. The reasons were as we would expect: identification of such problems as hyperlipidemia, obesity, hypertension and diabetes, with diet change instituted to help control these. In addition, a substantial number of people reported modifying their diets for general public health and preventive medicine purposes. Such changes were made more frequently in households of higher educational and income levels and where the adults were younger.

All this is, of course, reporting of self-described behavior. Are there "hard" data? Yes, and they are in several respects in keeping with these Department of Agriculture survey results. Thus, per capita consumption of eggs (the yolk is the single largest source of dietary cholesterol) has gone down steadily from its 1950 peak—down 30 percent by the late 1970s (Table I).[38–40] Per capita consumption of total milk fat solids has de-

clined by a like amount. At the same time—reflecting purchase at the supermarket of more and more fat-free and low-fat products (skim milk, 1 percent and 2 percent milk, low fat yogurt, ice milk, low fat cottage cheese)—consumption of nonfat milk solids has declined much less. And, over the decades, a remarkable change has occurred in the use of the visible fats (Table I, Fig. 4).[38–41] Since 1950, per capita consumption of lard—that is, pig fat—has gone down 80 percent and of butter, 55 percent, both reflecting continuation and acceleration of a decades-long downward trend. Margarine has come into increasing use. Its per capita consumption has doubled since 1950 alone and, in recent years, a sizable proportion of the total margarine is of the "soft" variety, that is, relatively low in saturated fats and high in unsaturated and polyunsaturated fats—a deliberate response of manufacturers and consumers to nutritional advice related to serum cholesterol reduction and prevention of coronary disease. Use of vegetable shortening has also increased, by 73 percent since 1950, and again there has been a change in composition, with an increasing proportion liquid, that is, relatively low in saturates and high in unsaturates. And, of course, all these vegetable fats—like all vegetable products—contain no dietary cholesterol. Finally, there has been a marked increase in use of vegetable oils, most of them, with the exception of coconut and palm oils, also relatively low in saturates and high in polyunsaturates. On the other hand, since World War II per capita consumption of meat—particularly beef—has gone up sizably, and the resultant increase in saturated fat and cholesterol intake has in part, but only in part, compensated for the sizable declines due to the trends in egg yolk, dairy fat, and the visible fats. Recently, initial data have become available from the U.S. Department of Agriculture 1977–78 Nationwide Food Consumption Survey involving 30,000 households. These include a comparison of 1965 and 1977 findings

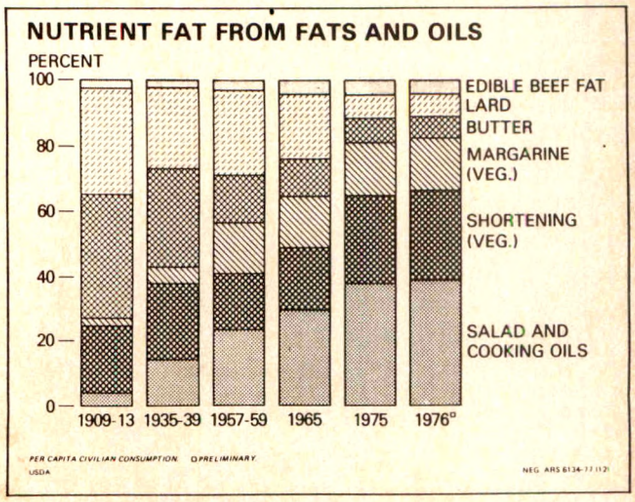

FIGURE 4. Nutrient fat from fats and oils (per capita civilian consumption). U.S. Department of Agriculture data.

(Table II).[42] In general, these are in agreement with the overall national food disappearance trends (Table I). However, a marked difference is to be noted in regard to beef, that is, decreased per capita intakes for young and middle-aged adults in the 1977 compared to the 1965 household survey, in contrast to the increase indicated by the disappearance data. (The Food Consumption Survey findings show a sizable increase per capita in beef consumption from 1965 to 1977 for male persons aged 15 to 18 and 19 to 22.) The household survey data indicate a considerable decline in percent of calories from total fat—from 45.1 percent in 1965 to 36.2 percent in 1977. The Department of Agriculture data therefore indicate that there have been modest but

TABLE II

Intake of Foods and Nutrients per Person by Age and Sex, 1965 and 1977, and Percent Change, 1977 Compared With 1965, U.S. Nationwide Food Consumption Surveys

	Intake per Person (g/day) by Age and Sex, 1965 and 1977, and Percent Change—1977 Compared With 1965																	
	Age 23–24 Years						Age 35–50 Years						Age 51–64 Years					
	Men			Women			Men			Women			Men			Women		
Food or Nutrient	1965	1977	%Δ	1965	1977	%Δ	1965	1977	%Δ	1965	1977	%Δ	1965	1977	%Δ	1965	1977	%Δ
Milk and milk drinks	318	243	−23.6	204	182	−10.8	236	203	−14.0	152	130	−14.5	203	180	−11.3	151	139	−7.9
Cheese	11	21	+90.9	10	19	+90.0	13	18	+38.5	13	18	+38.5	14	17	+21.4	14	19	+35.7
Eggs	55	38	−30.9	27	26	−3.7	51	41	−19.6	31	23	−25.8	51	36	−29.4	33	24	−27.3
Beef	110	89	−19.1	64	50	−21.9	102	79	−22.5	57	51	−10.5	81	74	−8.6	54	54	0.0
Pork	98	55	−43.9	54	32	−40.7	82	52	−36.6	50	32	−36.0	91	57	−37.4	49	30	−38.8
Poultry	32	31	−3.1	21	25	+19.0	33	32	−3.0	25	25	0.0	28	33	+17.9	25	27	+8.0
Fish	14	14	0.0	9	10	+11.1	13	17	+30.8	13	14	+7.7	18	22	+22.2	9	12	+33.3
Beef, pork, poultry, fish	254	189	−25.6	148	117	−20.9	230	180	−21.7	145	122	−15.9	218	186	−14.7	137	123	−10.2
Fats, oils	42	18	−57.1	23	15	−34.8	39	19	−51.3	23	14	−39.1	35	18	−48.6	24	15	−37.5
Calories	2,917	2,449	−16.0	1,803	1,616	−10.4	2,632	2,314	−12.1	1,652	1,514	−8.4	2,422	2,148	−11.3	1,619	1,522	−6.0
Protein	118.6	98.1	−17.3	72.3	65.9	−8.9	106.2	95.6	−10.0	68.3	63.9	−6.4	98.0	90.1	−8.1	67.4	65.2	−3.3
Fat	146.1	114.8	−21.4	86.5	73.7	−14.8	132.4	109.3	−17.4	80.2	70.8	−11.7	121.3	101.6	−16.2	79.9	71.2	−10.9

Δ = percent change: 1965–1977/1965.

TABLE III

Baseline Nutrient Intake Framingham, ND-HS and MRFIT Men

Nutrient	MRFIT (6,298 Men) 1977	Framingham (864 Men) 1970	ND-HS (1,196 Men) 1968
Calories per day	2,473	2,608	2,565
Protein (% of calories)	16.2	15.8	15.6
Carbohydrate (% of calories)	37.9	38.6	40.7
Alcohol (% of calories)	7.4	6.7	4.1
Total fat (% of calories)	38.4	39.0	40.4
Saturated fatty acids (% of calories)	13.9	15.0	15.6
Monounsaturated fatty acids (% of calories)	14.8	15.5	17.6
Polyunsaturated fatty acids (% of calories)	6.6	5.4	3.9
Cholesterol (mg/day)	450	530	533

MRFIT = Multiple Risk Factor Intervention Trial; 1977; ND-HS = National Diet Heart Study.

significant decreases in saturated fat and cholesterol intake by the American people.

The 1965 and 1977 household survey data also indicate a decreased intake of total calories by young adult and middle-aged American men and women. These data are intriguing in relation to the findings of the 1960–62 and 1971–74 Health Examination Surveys,[43] which indicate no change—possibly even a slight increase—in the sizable proportion of Americans who are grossly obese. Perhaps by the late 1970s, this situation was changed; this needs to be checked out.

One other trend merits attention: all the data indicate steady rises in per capita consumption of alcohol, and the epidemiologic evidence indicates a direct proportionality between average per capita consumption and prevalence of heavy drinking. This last phenomenon is of direct concern here because research in recent years has shown that heavy drinking is associated with higher prevalence rates of hypertension, independent of other traits related to risk of high blood pressure.[44–46] At this point it is also appropriate to note in passing that no data are available on trends of sodium consumption in our population.

Surveys of samples of the population indicate trends similar to those summarized earlier. Thus, comparison of the data on men volunteering for the Multiple Risk Factor Intervention Trial in the mid 1970s, and on men of the Framingham and National Diet-Heart Study surveyed a decade or so earlier indicate a modest decline in the 1970s in total fat, saturated fat and dietary cholesterol intake and a modest rise in intake of polyunsaturated fats (Table III).[47–49]

Serum cholesterol: In agreement with all these sets of nutritional data, surveys of the population indicate declines in average serum cholesterol levels toward more desirable goals (Table IV, Fig. 5).[50,51] Thus, repeated surveys in the late 1950s and early 1960s yielded average values ranging around 235 mg/dl for groups of middle-aged men. In the late 1960s and 1970s, the mean was 15 to 20 mg (about 7 percent) lower. Data are available indicating that these changes have been larger in the more educated than in the less educated strata of our population (Fig. 6).[51] Although these changes are still relatively modest, indicating that much remains to be done, they are all detectable in the population at large.

Cigarette smoking: The situation is similar in respect to cigarette smoking among adults, particularly those in the coronary-prone years from the 4th decade of life on. The prevalance of smoking in our population, at least in regard to men, peaked in the early 1950s and

TABLE IV

Mean Serum Cholesterol Levels of Middle-aged American Male Populations

Study	1950s to Early 1960s: Men Year	Age (yr)	n	Serum Cholesterol (mg/dl)	Late 1960s to 1970s: Men Year	Age (yr)	n	Serum Cholesterol (mg/dl)
Albany Civil Servant[b]	1953	40–59	1,712	231.4 ± 41.3[a]	1972	40–59	455	215.2 ± 32.8
Chicago Peoples Gas Co.[b]	1958–59	40–59	1,264	237.3 ± 46.1	—	—	—	—
Chicago Western Electric Co.[b]	1957–58	40–59	1,978	247.3 ± 53.5	—	—	—	—
Chicago Heart Association Detection Project in Industry[b]	—	—	—	—	1967–73	35–64	12,337	211.4 ± 36.5
Framingham Community[b]	1948	40–59	1,344	226.6 ± 43.0	1974	50–59	506	219.4 ± 37.4
Minneapolis-St. Paul Communities[d]	1966	45–54	630	232.9 ± 42.7	1975	53–62	628	222.6 ± 38.0
Northwest Railroad Workers	1959	40–59	2,424	230.5 ± 45.2	—	—	—	—
Tecumseh Community	1959–60	40–59	685	231.0 ± 42.3	1967–69	40–54	595	211 ± 35
U.S. Population (random samples)	1960–62	35–64	1,634	230.0 ± 48.0	1971–74	35–64	2,027	226.3 ± 45.9
Lipid Research Clinics (LRC)[c]	—	—	—	—	1971–76	35–64	11,708	209.3 ± 36.4
Multiple Risk Factor Intervention Trial (MRFIT)	—	—	—	—	1974–75	35–57	370,599	219.1 ± 40.6
All studies	1948–66	35–64	11,671	233.4 ± 45.3[e]	1967–76	35–64	398,855	216.8[e] ± 37.8[e]

[a] Standard deviation. [b] White males only displayed in these means. [c] Approximate value, based on reading mean value off graph for ages 35, 45, 55, 65 (195, 210, 215, and 215 mg dl, respectively). [d] Cohort analysis. [e] Unweighted mean.

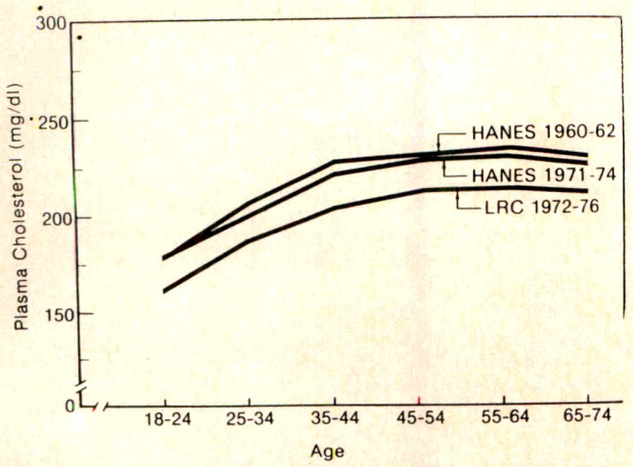

FIGURE 5. Mean cholesterol levels by age. Comparison of Health and Nutrition Examination Survey (HANES) and Lipid Research Clinics (LRC) survey.

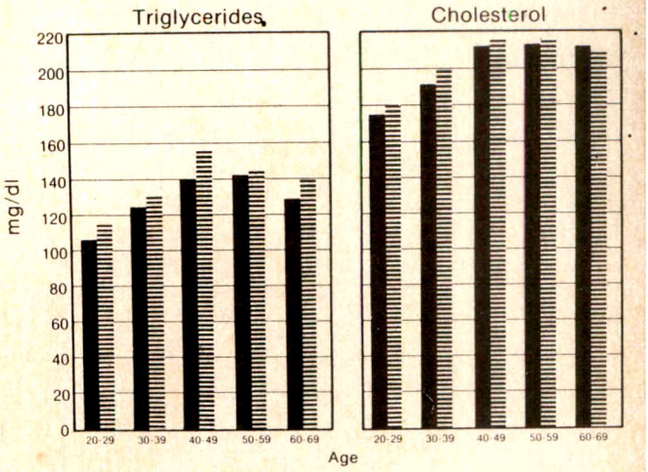

FIGURE 6. Plasma cholesterol and triglycerides for white men: comparison of high educational and occupational levels (**black columns**) and low educational and occupational levels (**hatched columns**). Lipid Research Clinics data. (Levy R, testimony before Subcommittee on Nutrition).

declined sizably even before the landmark *Report to the Surgeon General on Smoking and Health* in 1964. Thereafter the decline accelerated, particularly for adult men, so that by 1978 the proportion of men smoking cigarettes was at least 25 percent lower than in 1965 (Table V).[52,53] For both men and women, smoking has become a habit of a minority. Again, the higher the educational level, the more this is the case (Fig. 7).[52,53] These data clearly indicate that it is possible to impact the smoking situation, and that substantial progress has already been made. However, there are still big problems. Thus, the prevalence of heavy smoking—25 or more cigarettes per day—has apparently not yet decreased among adults.[52,53] And there is a big problem of smoking among teenagers, although data from the late 1970s indicate the beginnings of a decline.[54] And there is a special problem of millions of women who are smoking cigarettes and using the contraceptive pill.

Exercise: As you all know, one transformation—literally—in behavior in this country has been the large-scale adoption of leisure time exercise. Direct trend data on this are lacking as far as I know, although there are confirmatory data on sales of running shoes, tennis racquets, and so forth. Table VI gives the situation in 1977, and indicates that in this regard, as in all others, the change is more conspicuous among the more educated than among the less educated.[55] It is also greater among men than among women.

Control of high blood pressure: In the late 1960s and early 1970s, after publication of the landmark reports of the Veterans Administration antihypertensive drug trial,[56–58] it became increasingly a matter of concern that in the great majority of the millions with high blood pressure in our population the condition was undetected, untreated or uncontrolled.[59–61] This came to be known as the 1/2 by 1/2 by 1/2 phenomenon: about half the hypertensive population had their condition detected; about half of those whose condition was detected were being treated; and about half of those being treated had the condition controlled; that is, in only one in eight persons was the condition detected, treated and controlled. The Veterans Administration data on efficacy of treatment and the survey data on the low level of control were major foundations for the 1973 federal initiative establishing the National High Blood Pressure Education Program.[12] In the years since, the proportion

TABLE V

Estimated Percent of Current Regular Cigarette Smokers Among Americans Aged 17+ (Health Interview Survey, 1965–1978)

Year	All	Men	Women
1965	41.7	51.1	33.3
1970	36.9	43.5	31.1
1974	37.0	42.7	31.9
1976	36.7	41.9	32.0
1978	33.2	37.5	29.6
% decline 1965 → 1978	20.4	26.6	11.1

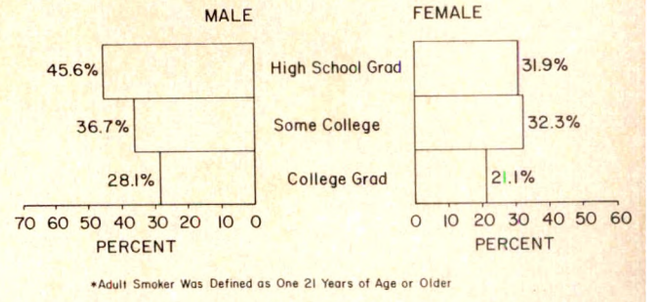

FIGURE 7. Percent of adults (age 21 or older) who smoke according to educational level. 1975 data, National Center for Health Statistics.

TABLE VI

Reported Exercise by Americans, 1977*

Stratum	Who Exercises? (%)	Who Jogs? (%)
All	47	11
Men	50	16
Women	45	7
Age		
18–29	60	22
30–49	47	10
50+	38	4
Education		
College	59	17
High school	47	11
Grade school	30	3
Occupation		
Professional & business	56	13
Clerical & sales	57	16
Manual	45	12

* Source: Gallup Poll.

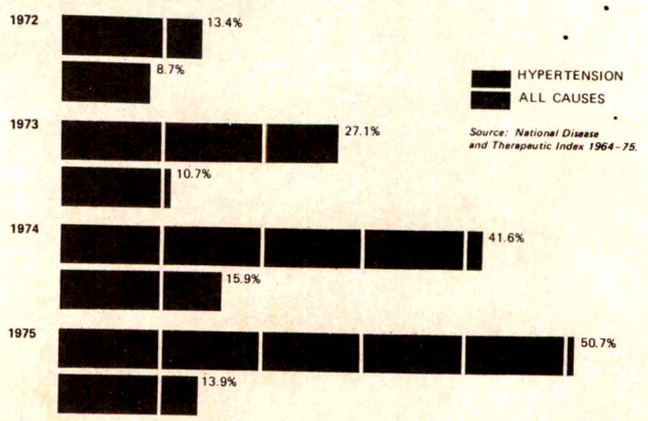

FIGURE 8. Patient visits for all causes and for hypertension and hypertensive heart disease (percent increase over 1971).

of hypertensive persons whose condition has been detected, treated and controlled has risen steadily. By the mid 1970s, it was approaching the 50 percent mark (Table VII).[60–63] However, I hasten to add that a substantial number of people with high blood pressure remain to be detected.

In agreement with the data on progress in the control effort, the number of patient visits to physicians—both first and repeated visits—for care for hypertensive disease has risen steadily, much more so than visits to physicians for all causes (Fig. 8).[63,64] A similar steady increase has occurred in the number of filled prescriptions for antihypertensive medication and the expenditure for such prescriptions (after correction for inflation).

The Possibilities for Prevention

Given these favorable trends among the American people in regard to the major coronary risk factors, how much of a decline in coronary mortality—and consequently in all causes of mortality, the bottom line—might be expected? A substantial decrease, based on extrapolation from prospective epidemiologic studies. Table VIII presents estimates based on the data of the national cooperative Pooling Project.[65,66] This is a conservative projection: a decrease in serum cholesterol of only 15 mg/dl, a decrease in mean diastolic pressure of the population of about 2 mm Hg due to improved control of hypertension, the reported decrease in percent of men smoking (Table V). The projected effect for white men of an average age of 50 is a 19 percent decrease in mortality due to coronary heart disease and a 13 percent decrease in mortality due to all causes.[67]

Data from two recently completed randomized controlled trials also give promising answers to this question: First, positive findings were reported from the primary prevention trial in Oslo, Norway, as presented last June to the European Congress of Cardiology in Paris.[68] The participants in this 5 year randomized controlled trial were nonhypertensive men aged 40 to 49 years, highly prone to the development of coronary artery disease because of hypercholesterolemia and cigarette smoking. Intervention with the experimental group involved nutritional recommendations to lower serum cholesterol, and—compared with the control men—the level was reduced 13 percent over the 5 years.

TABLE VII

Undetected, Untreated and Uncontrolled Hypertension, Chicago Heart Association (CHA) Detection Project in Industry (1967–1973), Hypertension Detection and Follow-Up Program (HDFP) (1973–1974), Community Hypertension Evaluation Clinic (CHEC) Program (1973–1975)

Diagnostic and Therapeutic Status at Screening	CHA (age 25–64 yr) (%)	HDFP (age 30–69 yr) (%)	CHEC (all ages) (%)
Not previously diagnosed, DBP ≥ 95 mm Hg	57	25	28
Previously diagnosed, not on treatment, DBP ≥ 95 mm Hg	18	21	11
Previously diagnosed, on treatment, DBP ≥ 95 mm Hg	13	16	17
Undetected, untreated or uncontrolled (sum of rows 1–3)	88	62	55
On treatment, controlled, DBP < 95 mm Hg	12	38	45
Hypertensive persons* (n)	6,089	36,304	220,217
Persons screened (n)	29,153	157,370	1,049,225

* Blood pressure at screening elevated, or positive history of diagnosed hypertension with current treatment and blood pressure at screening not elevated.
DBP = diastolic blood pressure.

Also, the men were advised to stop smoking; 31 percent did, compared with 19 percent of the control men. The 5 year incidence rate of coronary disease was reduced by 42 percent and the 5 year mortality rate due to coronary disease by almost 50 percent in the experimental compared with the control group.

Correspondingly, the Hypertension Detection and Follow-Up Program[69] recorded an overall reduction of more than 20 percent in mortality due to coronary and cardiovascular disease—and 17 percent in mortality due to all causes—in its Stepped Care group compared with its Referred Care group. A sizable proportion of the Referred Care group was treated; this was not a placebo-controlled trial. Therefore the significant result of this Program looms even larger in regard to the potential for prevention. As to its sizable stratum with entry diastolic pressures in the 90 to 104 range, and free of evidence of major target organ damage at entry, the most common type of hypertensive person in the population, almost 50 percent of all the hypertensive persons detected by the Program in its population screening, the result was even more dramatic: a reduction in all causes mortality of 28 percent—36 percent for the 90 to 94 substratum. These data, reported to the meeting of the College last March,[70] speak eloquently to the issue of ability to prolong life by the Hypertension Detection and Follow-Up Program Stepped Care regimen of vigorous sustained antihypertensive treatment to keep diastolic pressure below a normotensive goal.

The Decline in Mortality Due to Coronary Heart Disease

Well and good, then, as to the possibilities of prevention. What then has actually been happening "out there"? Figure 9 shows the course of coronary mortality

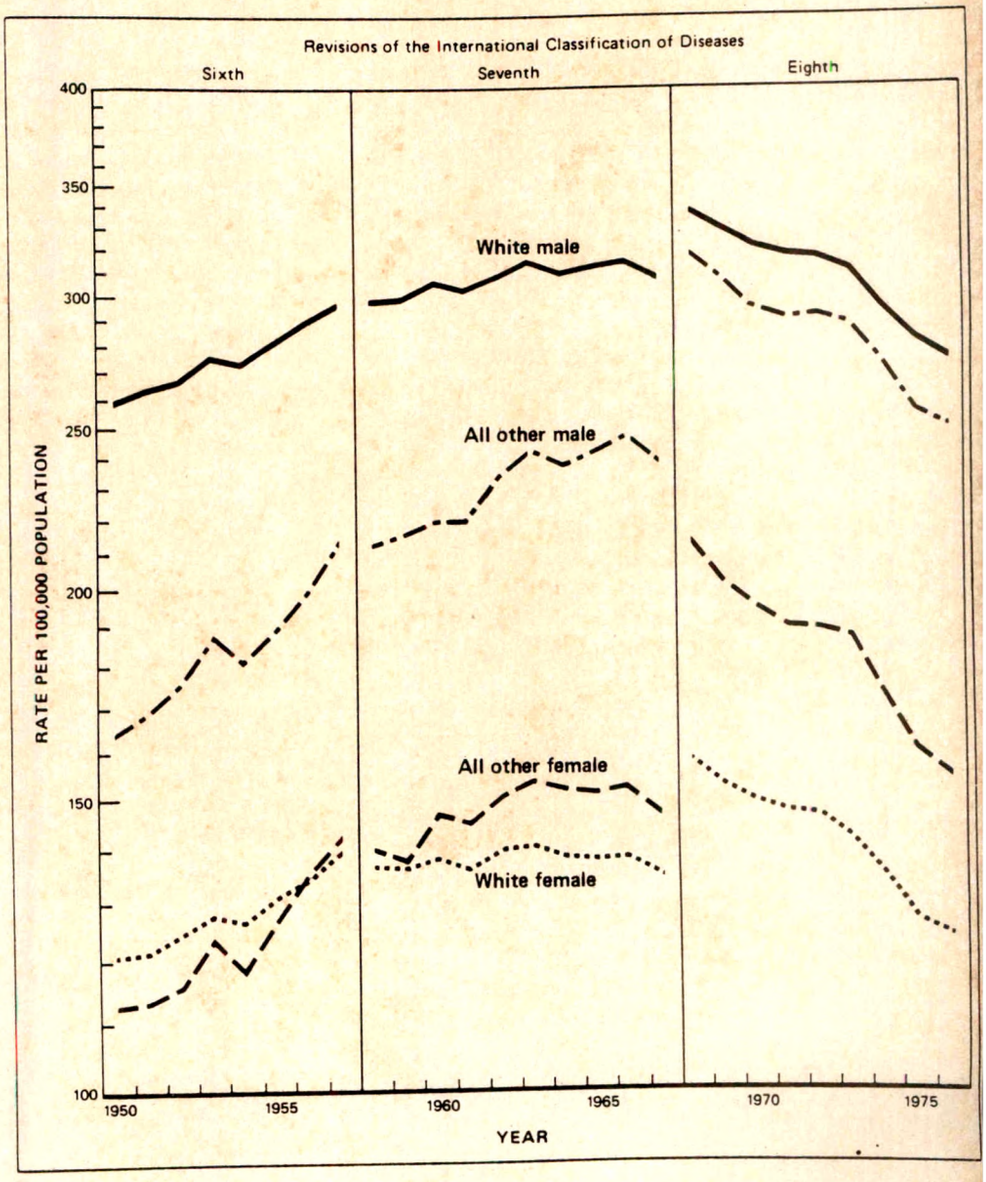

FIGURE 9. Age-adjusted death rates for ischemic heart disease, by color and sex (United States, 1950–1976), National Center for Health Statistics.

TABLE VIII

Expected Decrease in Coronary Heart Disease and All Causes of Mortality for Middle-Aged White American Men, Based on Reported Recent Changes in Population Risk Factor Status

Variable	Pooling Project (1950s)	Population Studies (mid 1970s)
Age (mean) (yr)	50	50
Serum cholesterol (mean) (mg/dl)	235	220*
Diastolic pressure (mean) (mm Hg)†	86.0	84.8
Cigarette smoking (%)	55%	40%
Expected 8.6 year mortality/1,000		
Coronary heart disease	50.4	41.7
All causes	120.4	105.7
Expected change in mortality/1,000		
Coronary heart disease	—	−17.3%
All causes	—	−12.2%

* % change −6.4 percent. † Percent of population hypertensive (diastolic blood pressure ≥95 mm Hg) in 1950s = 20 percent; percent of hypertensive persons detected, treated and controlled = 10 percent in 1950s, 50 percent in mid 1970s; mean diastolic blood pressure of persons with controlled hypertension = 90 mm Hg.

TABLE IX

Decline in Mortality Rate of Coronary Heart Disease, United States, 1968 to 1978 (persons aged 35–74, by sex and color)

Statistic	White Men	White Women	Non-White Men	Non-White Women	All
1968 rate	875.5	342.8	868.2	569.3	598.4
1978 rate	651.3	242.2	640.9	366.8	434.5
Difference	−224.2	−100.6	−227.3	−202.5	−163.9
% difference	−25.6%	−29.3%	−26.2%	−35.6%	−27.4%
Lives saved* 1978	65,246	32,961	7,592	8,109	113,908
Lives saved* 1969–78	317,743	170,119	39,596	40,592	568,050

* Based on expected deaths if the 1968 age-specific mortality rates had continued to prevail.
CHD—Coronary Heart Disease—ICD 410–413, 8th revision.
Rates, per 100,000 population, are averages of the rates for persons aged 35–44, 45–54, 55–64, 65–74.

in the United States since 1950—the steady rise, particularly for men, both white and black, that actually began in 1940 or even before—and then the dramatic break in the curve, the steady decline from 1968 on, continuing through 1978, the year of latest record.[71–73]

Table IX gives the details for persons aged 35 to 74 years, that is the age group being victimized by the epidemic of *premature* coronary heart disease: a decline of 26 percent for white and black men (in absolute units about 225 fewer deaths per 100,000 per year as of 1978) compared with 1968.[73] There are similar data for women. Overall, for all persons aged 35 to 74, there was a decrease of 27 percent, 164 fewer deaths per 100,000 per year. How many more persons aged 35 to 74 would have died in 1978 if the 1968 death rate had prevailed in that year? About 114,000—the lives that have been saved. And for the whole decade 1969 to 1978, a total of 568,000 lives have been saved.

Mortality rates due to stroke have declined even more dramatically (Table X).[73] And, given the decrease in coronary and stroke death rates, the "big two" among the major cardiovascular diseases, the death rate for that broad category has also fallen markedly, more so than for noncardiovascular diseases. The actual numbers merit attention: cardiovascular mortality down 28 percent, 235 per 100,000 fewer deaths in 1978 than 1968, about 164,000 premature cardiovascular deaths averted in 1978, and more than 800,000 lives saved from cardiovascular death over the decade 1969 to 1978—74 percent of all lives saved during those years. Despite the absolute increase in the population overall, and its middle-aged and aging segment, despite an increase of almost 2 years in the average age of our whole population, there was an absolute decline in all cardiovascular deaths, which peaked at 1,037,000 in 1973 and decreased to 962,000 in 1978 (Fig. 10).[73,74] *But,* these deaths are still too many—and still too many are occurring in the prime of life. *Our job is cut out for us.*

One study is available indicating that the decline in mortality may be part and parcel of a decline in incidence of acute myocardial infarction—as reflected by the trend of hospital admissions, in the Kaiser-Permanente system in northern California (Fig. 11).[75] Another data set—from New Orleans—indicates that in the 1970s, compared with almost a decade earlier, for both white and black men, severe atherosclerosis of the coronary arteries was less common at all ages from 25 to 44 (Fig. 12).[76]

A third study is in progress in Olmsted County, Minnesota; its results to date have been summarized by the investigator as follows: "I must repeat that we have not completed our comparability check, but it seems clear that there has been no change in the incidence of initial manifestation of [coronary heart disease] to parallel the decline in mortality."[77]

TABLE X

Decline in Mortality Rates, United States 1968 to 1978 (persons aged 35 to 74 years)

Statistic	Coronary Heart Disease	Cerebrovascular Diseases	Major Cardiovascular Diseases	All Causes
1968 rate	598.4	148.1	850.8	1,624.9
1978 rate	434.5	88.7	615.4	1,323.0
Difference	−163.9	−59.4	−235.4	−301.9
% difference	−27.4%	−40.1%	−27.7%	−18.6%
Lives saved* (1978)	113,908	40,248	163,520	216,206
Lives saved (1969–1978)	568,050	185,523	804,359	1,092,638

* Based on expected deaths if the 1968 age-specific mortality rates had continued to prevail.
ICD rubrics 410–413, 430–438, 390–448, 8th revision.
Rates, per 100,000 populations, are averages of the rates for persons aged 35–44, 45–54, 55–64, 65–74.

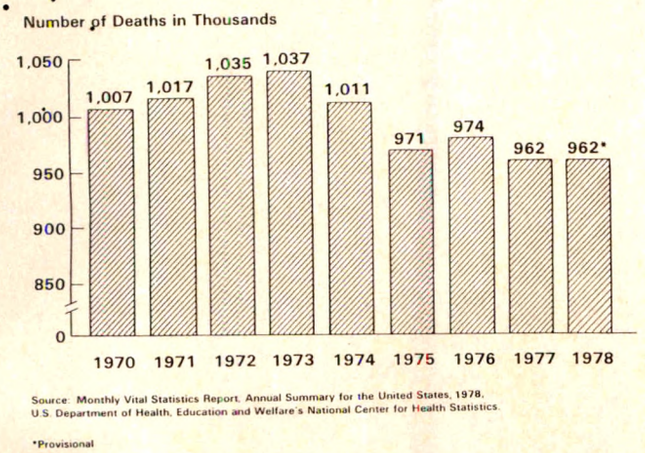

FIGURE 10. Toll of major cardiovascular diseases, 1970 to 1978.

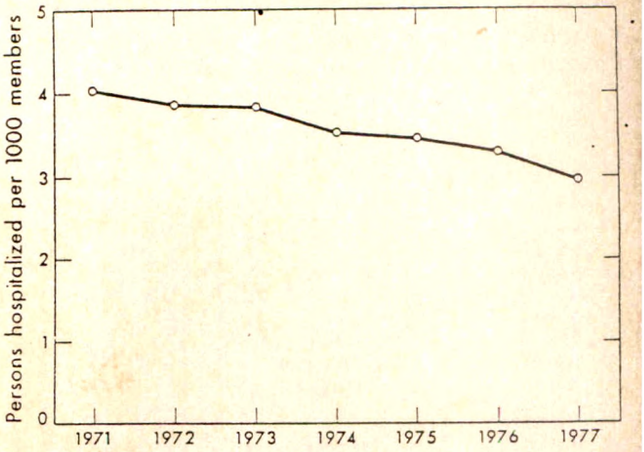

FIGURE 11. Age- and sex-adjusted proportions of subscribers, aged 35 to 84 years, hospitalized for acute myocardial infarction (International Classification of Diseases, adapted for the United States, code 410). Kaiser-Permanente Medical Care Program, northern California region, 1971–1977.

To the best of my knowledge, these are all the data so far available on U.S. trends of incidence of coronary heart disease and occurrence of severe atherosclerosis. We lack multiple data sets on these relevant trends—but two of the three cited pieces of information so far available are consistent with the massive data on the mortality trend.

In regard to decline in mortality, our country again has set the pace, as we have in the development of public policy and in beginning to improve life styles and control major risk factors. In 1968, our mortality rates due to coronary heart disease for middle-aged men were the highest in the English-speaking world. Thanks to the decline in mortality, by 1978 ours were the lowest, except for those of Canada—lower than the rates in Aus-

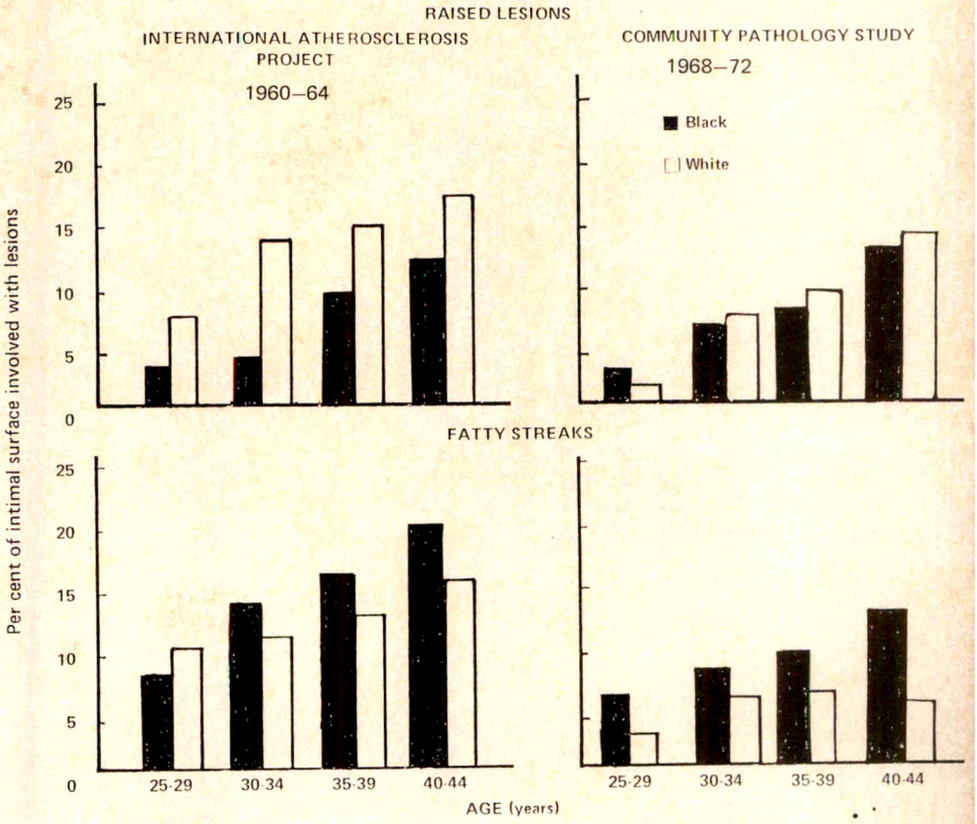

FIGURE 12. Atherosclerotic lesions in the coronary arteries of New Orleans men coming to autopsy, by study, race, age (basal cases). Reprinted from Strong and Guzman[76] by permission of the U.S.-Canadian Division of the International Academy of Pathology, Williams & Wilkins.

TABLE XI

Countries With Decrease or Increase in Rate of Mortality Due to Coronary Heart Disease (men aged 35 to 74 years, 1969 to 1977)

Country	1969 Rate	1977 Rate	Difference	% Difference
A. Countries With a Decrease in Rate				
United States	864.7	669.5	−195.2	−22.6
Australia	843.7	683.1	−160.6	−19.0
Canada	703.3	624.1	−79.2	−11.3
Israel	653.3	581.0*	−72.3	−11.1
Norway	582.9	537.1	−45.8	−7.9
Japan	126.3	102.6	−23.7	−18.8
Belgium	446.1	426.8*	−19.3	−4.3
Finland	893.7	878.0*	−15.7	−1.8
Scotland	813.7	808.6	−5.1	−0.6
Italy	313.0	309.6†	−3.4	−1.1
B. Countries With an Increase in Rate				
Bulgaria	299.3	423.5	+124.2	+41.5
Poland	186.5	307.7	+121.2	+65.0
North Ireland	782.4	867.1	+84.7	+10.8
Rumania	170.5	237.3	+66.8	+39.2
Hungary	441.6	499.2	+57.6	+13.0
Yugoslavia	185.0	227.6	+42.6	+23.0
Sweden	523.9	560.1	+36.2	+6.9
Ireland	662.2	697.7†	+35.5	+5.4
German Federal Republic	427.3	458.1	+30.8	+7.2
Austria	428.3	455.3	+27.0	+6.3
New Zealand	773.3	747.1	+26.2	+3.4
Switzerland	290.4	312.7	+22.3	+7.7
Netherlands	478.7	500.5	+21.8	+4.6
France	195.2	206.9*	+11.7	+6.0
Denmark	566.1	576.3	+10.2	+1.8
England and Wales	662.1	671.7	+9.6	+1.4
Czechoslovakia	587.9	590.4†	+2.5	+0.4

* 1976 data. † 1975 data.
ICD 410–14, 8th revision.
Rates per 100,000 population are averages of the rates for men aged 35 to 44, 45 to 54, 55 to 64, 65 to 74.

TABLE XII

Three Major Risk Factors and Risk of a First Major Coronary Event Between Ages 40 and 64 Years (8,162 White Men, Pool 5, Pooling Project, Final Report)

Quintile of Level	Events (n)	Risk of an Event per 1,000	Relative Risk	Absolute Excess Risk Per 1,000	Percent of All Excess
I	23	57.9	1.00	—	—
II	66	118.3	2.04	60.4	8.7%
III	107	168.0	2.90	110.1	15.9%
IV	167	241.1	4.16	183.2	26.5%
V	271	395.7	6.83	337.8	48.9%
All	634	221.0	—	—	—

$$\frac{\text{QII–V Excess Events, 4,000 Men}}{\text{All Events, 5,000 Men}} = \frac{691.5}{1,105.0} = 62.6 \text{ percent, of all}$$

events are excess events, attributable to the three major risk factors.

tralia, England and Wales, Ireland, New Zealand, North Ireland, Scotland (Table XI)[78]; yet, I hasten to re-emphasize, still too high, still at epidemic levels. A large group of countries—in eastern, northern and western Europe—is still registering increases in mortality rates due to coronary heart disease—trends related statistically to national trends of dietary lipid intake and cigarette use.[67]

Implications of the data: On the basis of the Pooling Project data collected in the late 1950s and 1960s in Albany, Chicago, Framingham and Tecumseh, the estimate can readily be made that high levels of serum cholesterol, blood pressure and cigarette use were responsibile, conservatively, for about two thirds of all

TABLE XIII

Serum Cholesterol, Blood Pressure, Cigarette Use at Baseline—Quintiles of Risk of a First Major Coronary Event, Based on the Three Major Risk Factors, Multiple Logistic Analysis, 6,875 White Men Aged 40 to 59 Years, Pool 5, Pooling Project

Quintile	Mean Serum Cholesterol (mg/dl)	Mean Systolic Pressure (mm Hg)	Mean Diastolic Pressure (mm Hg)	Mean Cigarette Use, Packs/Day: Mean All	Mean Cigarette Smokers Only
I	206.0 ± 36.2*	124.7 ± 13.6	78.5 ± 8.1	0.36 ± 0.65	1.08 ± 0.71
II	221.9 ± 37.1	131.1 ± 15.1	83.1 ± 9.1	0.85 ± 0.93	1.48 ± 0.77
III	234.3 ± 41.0	134.6 ± 17.0	85.1 ± 9.7	1.20 ± 1.04	1.73 ± 0.81
IV	246.5 ± 43.3	138.8 ± 18.6	87.9 ± 10.5	1.63 ± 1.06	2.02 ± 0.79
V	269.1 ± 53.9	151.1 ± 23.8	95.8 ± 13.7	2.05 ± 0.97	2.27 ± 0.74
All	235.6 ± 47.8	136.1 ± 20.0	86.1 ± 11.9	1.22 ± 1.11	1.84 ± 0.85

Quintile	Serum Cholesterol ≥220 %	Serum Cholesterol ≥240 %	Systolic Pressure ≥140 %	Systolic Pressure ≥160 %	Diastolic Pressure ≥90 %	Diastolic Pressure ≥95 %	Cigarettes 1/2+ Pks/Day %	Cigarettes 1+ Pks/Day %
I	33.8	17.6	16.9	2.1	13.2	3.1	33.2	17.1
II	52.6	30.8	29.0	5.9	28.3	11.9	57.0	41.1
III	63.6	42.7	38.6	10.0	37.1	14.6	69.6	56.7
IV	73.2	53.8	47.8	15.2	46.6	23.8	80.9	71.9
V	83.9	68.6	68.4	34.2	69.2	47.1	90.5	84.3
All	61.4	42.7	40.1	13.5	38.9	20.1	66.2	54.2

* Standard deviation.
Pks = packs.

major coronary events among the middle-aged American men in that set of cohorts. These are the excess cases, attributable to the major risk factors (Table XII).[65,66] The implications of these data are obvious: Our coronary rates would be lower by two thirds if all middle-aged American men had levels for these major risk factors like those of the lowest quintile (20 percent) of coronary risk in our population; that is, if our *overall* mean serum cholesterol level was about 205 mg/dl, not 235; if our *overall* mean blood pressure was about 120/80 mm Hg, not 136/86; if none, or almost none of us smoked cigarettes regularly (Table XIII).[66]

Over the last decade or so, we have been moving toward these more favorable goals, the more educated among us more so than the less educated—at least in regard to serum cholesterol and cigarette use. And in American men aged 35 to 74 years, the rates of coronary disease have declined by more than 25 percent. Moreover, data are available from the Metropolitan Life Insurance Company indicating that the decline is greater for the more educated than for the less educated.[79] This is of course the expected finding, given the greater degree of change in lifestyles and lifestyle-related risk factors in the more educated than in the less educated, if these changes are playing an important role in the mortality decline. That is, these data give further weight to the widely held estimate that the changes in life style and life style-related risk factors have made a key contribution to the decline in mortality due to coronary heart disease.

Given the trends over the last 10 years, I am prepared unabashedly to propose a goal: continue to work to reduce the still high death rate due to coronary heart disease by 3 percent a year over the decade of the 1980s, so that by 1990—compared with the peak in the late 1960s—the total decline is close to 60 percent, that is, close to the figure the Pooling Project data indicated as possible.

Conclusion

These data—together with all the other scientific evidence, and all the findings on what has happened over the last 20 years—are consistent with the conclusion that we have been on target in undertaking and developing the coronary prevention effort over the last 20 years. It is a reasonable inference, given all the facts, that the positive changes in lifestyles and risk factors among Americans relate causally to the decline so far registered in the coronary mortality rates. This is not only a reasonable inference from the facts, but also a reasonable conclusion based on fundamental theoretical grounds, that is, the basic generalization that epidemic disease is due to ". . . disturbances of human culture," to quote Virchow,[80] so that amelioration of these ". . . disturbances" induces abatement of the epidemic. Of course, it is very hard unequivocally to prove the validity of that inference. But in that regard, I call to your attention the sage remark of Darwin[81] on the shortcomings of excessive skepticism:

> I am not very skeptical,—a frame of mind which I believe to be injurious to the progress of science. A good deal of skepticism in a scientific man is advisable to avoid much loss of time, but I have met with not a few men, who, I feel sure, have often thus been deterred from experiment or observations which would have proved directly or indirectly serviceable.

My conclusion then is that there is good reason to keep on doing what we have begun to do—to do it more so and even better—and that is what this Conference is all about. Our purpose is humanism—longer life with better health—in the best Hippocratic traditions of medicine, in the spirit that Pasteur[11] put so well in these inspiring words:

> To him who devotes his life to science, nothing can give more happiness than increasing the number of discoveries, but his cup of joy is full when the results of his studies immediately find practical applications.

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Changing Behavior for Health

DAVID A. HAMBURG, MD

On an occasion like this, we are concerned very much with the moving frontiers of science. We are not talking about freezing 1980 once and for all with respect to the prevention of coronary heart disease—let alone the behavioral component, which is, after all, a new field. The moving frontiers involve new information about risk factors and disease; there will be greater specificity in the future about what risk factors have what kind of relation to ultimate outcomes. I think there will be, particularly in the emerging area that some people call ecogenetics, better ways of specifying individuals at particularly high risk and therefore, among other things, of focusing behavioral interventions on people who are in greatest need of those interventions.

Behavioral Aspects of Health

In my mind, the decrease in cardiovascular mortality is one of the great stories of the modern era, as was the earlier prevention of rheumatic heart disease. I see much potential for further improvement in our capability to prevent cardiovascular disease, in light of scientific advances and their judicious application. Some of that has to do with the difficult general question: Can behavior change? We have some reasons to believe that in this sphere behavior can change, despite all the inherent difficulties of modifying gratifying patterns to which people are more or less addicted.

The National High Blood Pressure Education Program[1] is encouraging in that regard. The survey data on exercise, which can readily be confirmed by looking around us, are quite dramatic. Everybody is out jogging and playing tennis; you don't have to go very far to see that this is a behavior that has changed a good deal in recent years.

As for the role of physicians in changing behavior for health, I believe that role has been somewhat underestimated. And the key factor in it is the still enormous respect in the society at large for physicians and, in the world at large, for American medicine. That respect gives leverage that is virtually unparalleled for changing behavior in healthful directions.

We have in recent years seen a sea of change in medical and public awareness of the behavioral aspects of health and a tidal wave of new scientific developments in behavioral biology. These in turn are having a stimulating effect on a wider range of behavioral sciences. There is now certainly a broad awareness of behavioral factors pertaining to smoking, alcohol use and traumatic injuries—indeed, in relation to the etiology and pathogenesis of diseases and disabilities that constitute a large part of the burden of illness in this country.

We may have been a little slow to face up to aspects of these issues, but we are doing so now. In the Institute of Medicine, we have tried to respond to that heightened awareness of behavioral factors by seeking ways to strengthen the scientific capabilities that had, to a considerable extent, been neglected for a long time.

These problems are inherently interdisciplinary. Just a few weeks ago we published a report on scientific opportunities in alcohol problems,[2] a very exciting refutation of the conventional wisdom that there is no handle on the alcohol problem. The report deals with both biologic and social factors, as must be done in all major behavioral aspects of illness. Another study, on stress problems, will be out in a few months.

The third major study of the Institute will not be published until next year. Called "Health and Behavior, A Research Agenda," it is based on the six conferences of our Institute. Proceedings of the first conference, on smoking and behavior, have been published.[3] The second, still in preparation, was on the interaction of pharmacologic and psychosocial interventions, focusing on three major concerns, hypertension, diabetes and depression. Proceedings of the third conference, on biobehavior factors in sudden cardiac death will be published shortly. I need hardly say that the National Heart, Lung, and Blood Institute has had an important role in stimulating and fostering those studies.

The emergence of behavioral biology is an invigorating development in this field. It is not really my topic, although it has been a large part of my career. I just want to mention in passing that it seems to me that one of the crucial linkages in the biomedical and behavioral sciences occurs in a sort of final common pathway, namely, the brain's control, or at least strong regulatory influence, over the endocrine and autonomic nervous system.

When I was a student, we were taught that the endocrine and autonomic nervous systems were largely independent of central nervous system control. We now know how wrong that was. The great coordinating systems in the organism are two: the nervous system and the endocrine system. Work of recent years on hypothalamic hormones has shown specifically and tangibly the coordination of the coordinators, the neuroendocrine linkages, in directing the adjustments of the organism to changing conditions. But the research on hypothalamic hormones not only provided profound new insights of great intrinsic interest, but also a remarkable technology for peptide analysis.

Taken together, these advances, coinciding with the discovery of receptors in the brain and other related progress, have produced an explosion of neuropeptide discoveries in the past few years. I think that these discoveries have at least dimly foreseeable implications for our understanding and capacity to make useful in-

terventions over the next decade or two in various domains of health, disease and behavior. For example, there will be future implications for sexuality, alertness, pain relief, sense of well-being, relief of anxiety and depression, regulation of appetite, lowering of blood pressure, modification of learning and memory and a variety of cardiovascular and gastrointestinal effects.

I am not saying that the new pharmacology is here; I am saying that it is, to a certain extent, foreseeable and is likely to be much more specific than the old pharmacology, and has a very important potential in the current thrust of behavioral biology. In fact, an unprecedented array of molecular cell systems, techniques and concepts are now available for research on problems of behavioral medicine that would have been unimaginable 15 or 20 years ago. It is safe to predict a transforming effect on the field in perhaps another 15 or 20 years.

Social Learning and Cardiovascular Risk Factors

I shall devote the rest of my time to a discussion of learning and cardiovascular risk factors. It is, after all, the extraordinary human learning capacities that we are concerned with in talking about changing behavior for health. It would be surprising indeed if this most distinctive of all human characteristics, this learning capacity that so far outstrips that of any other species, could not be oriented toward what are in effect survival interests and concerns of the human species. It is true that the scientific approach to these questions is very recent, and most of the work has to be viewed as path-breaking and exploratory, but I call your attention to some promising and illuminating lines of inquiry that may have potential for future application.

Success in management of patients, let alone in prevention, depends in part on our understanding of human behavior. The scientific basis for our understanding of behavior and modifying it has been greatly strengthened in the past few decades by the emergence of authentic principles of learning based on experimental research in animals and human beings. Such analysis is concerned with identifying stimuli, especially rewards and punishments, that influence behavior. Understanding has increased with respect to stress and coping and with respect to the interaction of persons with their environment, particularly the social environment and the role of the social influences on behavior. The principles of learning have been utilized in recent years in new approaches to cardiovascular risk factors such as smoking and obesity.

Progress in research has demonstrated that behavioral intervention can be effective, but it is far from precise in terms of determining how effective it is for whom and under what conditions. A great deal of sorting out needs to go on. Such interventions are being tested not only in weight control and smoking cessation but also in promoting adherence to medical regimens. The emergence of a sizable cadre of behavioral investigators addressing problems like obesity is a very recent development, and the numbers are still far from satisfactory. The manpower need is great.

Obesity: Let me briefly summarize some prominent features of the work on obesity, a very tough area, but an important one. Much of the early work had important methodologic limitations. There is no question that behavioral strategies based on learning principles can be effective in achieving short-term weight loss. I emphasize short term. Patients in weight loss programs utilizing such strategies manifest a great deal of variability in their responses to treatment. Attempts to identify predictors of such variability have not been very successful. The magnitude of weight lost over the long term in most of the regimens has been marginal. With respect to clinical significance, evaluations of long-term maintenance are badly needed and, indeed, focus on continuing reinforcement for maintenence is a crucial direction in both clinical practice and research. Several trends are discernible in the newer crop of studies. One is a closer integration of behavioral and physiologic variables. Another is increased attention to physical activity, along with attention to eating behavior.

A wide range of psychological factors is being considered, especially those having to do with self-respect and alternative gratification. More rigorous experimental methods are being used as well as long-term follow-up and—points I want to emphasize—growing attention to the social factors that influence obesity and to prevention in childhood and adolescence. These latter trends are exemplified by the component on obesity in the Stanford Three Community Study.[4] This study relied heavily on principles of social learning, which I think is a very important concept. There was a component on dietary modification and reduction of obesity. The results suggest that significant dietary modification can be achieved through a large-scale community approach using both mass media and face to face intensive instruction components. This particular finding is now stimulating research efforts to influence persons through their home and work environments over their lifetime, rather than treating obese persons in isolation, which is a very discouraging enterprise. In planning community-wide educational programs, it is reasonable to focus on persons most likely to benefit from the best weight. That would mean moderately overweight adults, adolescents and children.

Smoking: With smoking, as with obesity, the task of interrupting a gratifying behavioral pattern on which the individual has become highly dependent is very difficult. We have to face it. It is harder than prevention by, say, cleaning up some foul-smelling sewers. But we have scarcely scratched the surface of what modern biobehavioral science might be able to do in this regard, since so few well trained investigators have addressed these problems.

There are three critical issues in smoking cessation research. One is improving intervention techniques and research methods, especially to prevent relapse. Another is providing the majority of smokers who want to quit with minimal outside aid. Another is focusing treatment on special groups of smokers, including pregnant women and women of child-bearing age, blue collar workers,

olunteers, persons who are medically at risk, and adlescent smokers. The workplace has come to be viewed s a promising site for intervention, with respect to both essation and prevention. I think that this area deserves nuch more vigorous pursuit now. Most adult smokers an be reached in the workplace.

Among men who smoke, the problem is heavily oncentrated among blue collar workers. They tend not o seek outside help, although surveys indicate their esire to stop smoking is similar to that of other smokrs. Working women smoke at a somewhat higher level han do women in the home. Workers in occupations nvolving asbestos, coal mining and cotton have a special levation of risk when they are smokers. The workplace rovides an environment for long-term social reinorcement. I emphasize the value of long-term social einforcement in maintaining nonsmoking behavior.

The critical problem for smoking cessation is naintenance of nonsmoking behavior over the long erm. Here again, lessons have been learned from the tanford heart disease prevention research.[4] Three ears after the program started, the proportion of mokers had decreased by 3 percent in the control ommunity, about 8 percent in the community in which moking education had been limited to use of the media nly and by 24 percent in the community receiving ersonal counseling as well as education through the nedia. Fifty percent of the high risk smokers receiving ace to face counseling had stopped smoking, compared vith 11 percent exposed to the media alone.

In the effort to obtain long-term smoking cessation, t is useful to compare the characteristics that distinuish abstainers and relapsers. The abstainers over the nger term tend to have a higher sense of efficacy as a erson, sense of worth as an individual and personal ommitment to the task; very importantly, they have nore social supports for smoking cessation, including nodels of coping provided by ex-smoker peers. These indings have implications for our preventive program. think we are moving away from a view of the individual ssentially in isolation in the short term to a view of the ndividual in a social context over the longer term and he role of the physician in facilitating the social suports to provide continuing reinforcement for healthmproving behavior. Here lies a great challenge to us ll.

The relapse rates in some studies have been reduced y buddy systems, peer support, interpersonal recogition for abstinence and the experience of helping thers to quit. That is an interesting point. In a number f spheres, the sense of having overcome some difficulty, t least for a while, and of being able to be useful to thers in overcoming the same difficulty is a very gratying one.

Finally, we are seeing increasingly the teaching of pecific coping responses, ways of handling particular tuations. This leads me to a more explicit considertion of the social factors, including influences of peers, arents and teachers, through instruction and example, eward and punishments. Some of these influences mpete with one another. For example, information about the dangers of cigarette smoking is in competition with observation of cigarette smoking in parents, teachers, and peers, that is, the attractive modeling of cigarette smoking. Also, the glamour depicted in advertising for cigarette smoking acts to overcome fears of its danger to health, so that the challenge of influencing cigarette smoking has brought about efforts to prevent children in early adolescence from becoming cigarette smokers. That seems to be a crucial area. Although adolescent smokers believe that cigarette smoking is unhealthy, this belief can be outweighed by peer pressure, models of smoking parents and attractive messages in models in the mass media.

Information is of value if it comes from a credible and respected source, but I think we have to go beyond the mere giving of information to training how to cope with social influences on smoking behavior. Training adolescents to resist social pressures is a focus of some interest now—specific instruction on ways to resist persuasive communications. Some programs are using videotapes to show adolescents in common social situations, focusing on short-term incentive such as kissing. How unattractive it is to kiss a smoker seems to carry more weight with a lot of adolescents than talking about what might happen 20 or 30 years downstream. These programs include a lot of practice in actual situations or simulated situations that involve resisting social pressure to smoke, a kind of inoculation against social pressure to smoke. The onset of adolescence is a critical period of biologic and psychosocial change. The adolescent years are highly formative for health-relevant behavioral patterns such as smoking, patterns of food intake, patterns of exercise, and so on. It is a period characterized by exploratory behavior. A lot of things are tried out, and some of the various patterns tried out become enduring patterns of behavior. Thus, health intervention programs in this period have a high potentiality for increasing the likelihood that the patterns will stick, will become enduring ones, consistent with the maintenance of good health.

But is has been historically difficult. We have not known very well how to communicate with adolescents, and these young people have fallen between the stools in health services, between pediatrics and medicine, between adult and child psychiatry. The potential of the school programs in health in the new era has yet to be fulfilled. One program involves peer counseling—that is, training peers to work together, providing continuing supervision.

Peer counseling approach: Instruction and content of peer counseling programs may differ. Some of the content in programs I have been connected with involves the tasks and strategies of that particular circumstance in which people find themselves in phases of the life cycle, setting ways of coping with the experiences that they find distressful, particularly aspects of human relation that are so crucial to all of our lives. There is certainly some indication that good peer counseling programs can be beneficial to both the counselors and counselees. Some studies over the past few years have taken this peer counseling approach,

which arose in other contexts, and applied it to the onset of tobacco dependency. There are field experiments, for example, in which 16 year olds communicate skills to 12 year olds—for example, resisting peer pressure—with hundreds of students in matched experimental and control schools. These groups have been compared on cigarette smoking rates at the start of the program with follow-up periods not exceeding 2 years.[5,6]

The results are encouraging to this point. There is much less smoking among the adolescents exposed to peer counseling programs than among the control groups. Of course, the advantage of peer counseling is the great credibility of peers, one adolescent talking to another, but adult guidance and, preferably, medical guidance are needed in these peer counseling programs.

Community-Based Studies and Programs

Let me come back for just a moment to the Stanford Heart Disease Prevention Program, because it was one of the path-breaking studies, and it had more behavioral science sophistication than many of the others and provided considerable insight into behavioral change. The key aspects of this field experiment were the following: (1) The design of the campaign was based on an analysis of the knowledge deficits and the media consumption patterns of the intended audience—that is, meeting the needs of the local people in a comprehensible way; (2) the mass media approaches and the face to face instruction were based on established principles and methods of behavioral science, especially those of social learning; (3) the mass media materials were devised to teach specific behavioral skills—for example, preparation of a palatable low fat diet as well as offering health-relevant information and motivating people to use that information for their own benefit.

There was a 30 percent reduction in overall cardiovascular disease risk, although there are no specific data on the health outcomes—myocardial infarcts, and so forth—but there was risk factor reduction. It is noteworthy that the intensive individual instruction of high risk persons added to the media effort provided an extra benefit. There are hints in that experiment that these effects are probably better sustained if community leaders and family members are involved, thus building a social support network that can provide continuing reinforcement for healthful behavior.

Other studies have pursued different aspects of this problem in a more differentiated way. For example, Blackburn's study has differentiated results of the effects of different media for different audiences.[7] The Pennsylvania study is going much more deeply into matters of community organization.[8]

The famous study in Finland, which does have data on some health outcomes as well as on risk factor reduction, involved a comprehensive community program, really comprehensive—using mass media, general health education measures, provision of practical services, training of local personnel, environmental changes, and installation of communication and information systems.[9] It elicited a remarkable degree of cooperation from both industry and government. And one has to say that the results of the project are encouraging. So many things were done that it is hard to single out one or two key factors in it, although my impression is that the results indicate the effectiveness of social networks in diffusing information, initiating behavioral change and maintaining reduction in cigarette smoking, serum cholesterol levels and blood pressure levels.

The potentially important Oslo study gives further encouragement in this regard.[10] It was effective in lowering two major risk factors in its participants, hypercholesterolemia and cigarette smoking, and it has data indicating a sizable reduction in coronary incidents and mortality. I would like to know more about behavioral interventions, since they seem to have been beneficial with respect to smoking and hyperlipidemia in healthy, normal middle-aged men. Particularly if it turns out that their health outcome measures are indeed positive, it will be important to learn in detail the nature of the behavioral interventions, which have not yet been published.

Components and tasks of community-based studies: In all of these community-based studies, which involve some mixture of broad public education and medical prevention, there are several tasks that deserve special attention. This is my reading of what at least are some of the factors that cut across the Stanford, Oslo, North Karelia and other studies in this field. (1) Providing specific, comprehensible information regarding the nature of the threat to health. (2) Providing specific, comprehensible information about the skills helpful in coping with the risk factors—what can you do. (3) Prompt reinforcement of early changes of behavior toward health-promoting patterns. (4) Community organization in ways that provide respected models in the community of health-promoting behavior and long-term social reinforcements for such behavior. (5) Involvement in health education of not just the individual alone but the family. (6) The formulation of educational messages in such ways as to link health-promoting behavior with self-respect—a key aspect of human experience—self-respect in the sense of personal worth and of course motivation fundamental to survival. (7) Utilization of school and work sites. (8) Utilization of specific media for specific audiences. For example, the radio is very significant for adolescents.

In practice, such interventions—I would say categorically—will profit in general from physician leadership, physician leadership in the spirit of collaboration with community organizations and the educational sector including the media. Overall, such programs have to be concerned not only with the general population but with specific sectors of the population like adolescents or the black community and then with the individual.

Role of Stress and Social Support Systems

I shall close with a word about another insight into social factors and a little bit more about human relations, especially the deep attachments among people that are such a crucial part of the human experience

altogether and seem increasingly to have relevance to various diseases. From various epidemiological studies of different designs in different countries, in different populations with different health outcome measures and stress indicators, there has been impressive convergence of evidence indicating that many disorders are precipitated by environmental stresses such as moving, unemployment and bereavement.

A recent report of unusual interest in this context is one from the Human Population Laboratory in California, looking at the ties between social linkages and mortality, Berkman and Symes' work[11]—a random sample of about 7,000 adults with a subsequent 9 month mortality follow-up. People who lacked social attachments were much more likely to die in the follow-up period than were those with extensive contacts. And, surprisingly to me at least, this finding seems to be independent of the known major risk factors.

Natural support systems can be effective in buffering stressful experiences. They also can influence the use of health services and adherence to medical regimens. This is pertinent to the requirements for behavioral change and prevention, smoking cessation, weight control or long-term adherence to antihypertensive medication.

It is also very important for the prevention of health-damaging behavior, because social support systems facilitate the development of coping strategies and help people contain emotional distress, maintain self-respect, preserve relations with other people, meet the requirements of new situations and prepare for the future. Thus an important opportunity in medical practice is to help patients mobilize latent support systems—for example, family, friends, community resource people. In so doing, we may become increasingly effective in changing behavior for health.

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Task Force 1: The Physician and Children (Pediatric and Adolescent Practice and the School)

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I. Introduction

Physicians who take care of the child have long recognized and acted on two premises:

A. Events that occur from birth through adolescence may provide the template for the adult and his state of health.

B. Promotion of good health improves that template, and thus prevention of disease becomes a high priority in the care of children.

These physicians have learned over the past decade that there is now a role to play in the prevention of atherosclerosis and of coronary heart disease, the greatest killer of adults in the United States. The physician who takes care of the child has learned about the risk factors that are linked to heart disease in the adult. Investigation among childhood populations has indicated that habits set in childhood lead to the presence of risk factors in adult life. In some children, these risk factors are already present. *The major risk factors are:*

A. Elevated levels of serum total cholesterol and low density lipoprotein cholesterol.

B. Elevated blood pressure.

C. Cigarette smoking.

Prevention of the development of these risk factors in the child and intervention to control them where present hold promise for substantial improvement in the good cardiac health of the adult.

The physician who takes care of the child should encourage each individual patient and family to assume responsibility for protecting his or her and their own health. Health promotion is the process of fostering awareness, influencing attitudes and identifying alternatives so that an individual and family can make informed choices and change behavior to achieve an optimal level of physical and mental health and an improved physical and social environment.[1]

The physician promotes, through health education, the imparting of factual information, but additionally makes planned attempts to improve health-related behavior.[2] There are many ways the physician can educate patients and their families. For maximal effect, methods should stimulate the individual patient's involvement in health maintenance rather than just attempt to convey knowledge. Transfer of knowledge by itself does not necessarily result in better health and improved quality of life.[3,4]

The purpose of this report is to guide physicians who take care of children as to what is known, how they may play a role in influencing the risk factors that may threaten cardiovascular health in adulthood, and where and by whom such preventive efforts should be pursued.

II. Current Knowledge

A. Risk Factors

1. Elevated serum cholesterol levels: Mean serum cholesterol levels of 100 to 150 mg/dl are found in children in most areas of the world where there is a small incidence of coronary artery disease in adults. These compare with mean levels of 150 to 200 mg/dl in the youth from populations where there is a large incidence of coronary artery disease in adults.

Mean levels of total cholesterol of 150 to 180 mg/dl in adults in the population are consistently related to the lowest rates of coronary artery disease, and average cholesterol levels of 120 to 160 mg/dl for children may be necessary to achieve these optimal adult levels.[5] Differences in diet appear in part to be responsible for population differences in serum cholesterol levels.[6]

The level of serum cholesterol in an individual is affected by several interrelated factors, including genetic differences in metabolic pathways[7] and in responses to cholesterol and saturated fat in the diet.[8,9] In children in whom a cholesterol metabolic pathway abnormality is a strong factor, it may not be possible to lower the serum cholesterol to the desired level with diet alone. There are individual differences in the strengths of these two factors, and these affect the response of serum cholesterol to restriction of cholesterol and saturated fat in the diet.

Distributions of lipid-lipoprotein levels in the childhood population are now available.[10] A child's lipid level may now be followed sequentially according

to percentiles for age. Routine and community mass screening of serum lipid levels in children is not recommended. However, children from families with a history of premature myocardial infarction (before age 60 years) have an increased risk of having hyperlipidemia and should be screened.[7,11,12] Children of families with known hyperlipidemia or a strong family history of hypertension, or both, should also be studied.

Cholesterol is distributed among the lipoprotein fractions, most being carried by low (LDL) and high (HDL) density lipoproteins. Risk of coronary artery disease in the adult is probably related particularly to the low density lipoprotein level. Population studies suggest that high density lipoprotein levels have a protective effect in regard to development of atherosclerosis.[13,14]

If a child from a high risk family has two elevated serum total cholesterol measurements, lipoprotein fractions should be measured to determine the distribution of total cholesterol among the lipid fractions. This information may be useful as more is learned about factors affecting cholesterol distribution among the lipoprotein fractions. However, it is premature to give prognostic significance to elevated HDL cholesterol levels in children; for the present, attention should be directed toward total serum cholesterol level and LDL cholesterol.

2. Elevated blood pressure: The definition of hypertension in a child or adolescent is understandably arbitrary. All would agree that definite hypertension is present if the criteria of the World Health Organization are fulfilled, that is, systolic or diastolic pressure, or both, is repeatedly 160/95 mm Hg or higher. Hypertension at this level in preadolescence carries at least as great a health hazard as it does in adulthood, and every effort should be made to find any known cause. Interest is now being focused on children and adolescents who have average blood pressure measurements in the higher distribution deciles for age and sex, borderline hypertension or high normal levels.

A recent study has shown that American white men aged 40 to 59 years with a diastolic blood pressure between 80 and 88 mm Hg have a 42 percent greater risk of coronary artery disease than do those with a diastolic pressure equal to or less than 80 mm Hg.[12] Another study[15] of adults who as teenage boys had a systolic blood pressure equal to or greater than 130 mm Hg showed an increased risk of coronary artery disease in later years compared with those whose systolic pressure had been less than 130 mm Hg.[15]

Borderline hypertension has been defined as systolic or diastolic pressure, or both, at or above the 95th percentile of the distribution for age and sex on three repeated measurements, and absence of a secondary cause.[16] An alternate definition is the World Health Organization definition of adult borderline hypertension: blood pressure of 140 to 159 mm Hg systolic or 90 to 94 mm Hg diastolic.

Epidemiologic data suggest that at least some children with transient "spikes" of blood pressure into the hypertensive range continue to have blood pressures at this level through pre-adult and adult years.[17–19] However, not all children and adolescents with such "spikes" will later have sustained hypertension. One longitudinal study[20] of young adults with this phenomenon revealed that on follow-up study almost 80 percent were normotensive, about 10 percent had continued "spiking" and another 10 percent had sustained hypertension. The Muscatine, Iowa study[21] showed that of children who had elevated blood pressure at or above the 95th percentile on a single measurement, fewer than 1 percent were found to have persistent blood pressure elevations on repeated examination and more than half of these were obese. It is not possible at present to predict which children and adolescents with blood pressure "spikes" are at risk of having sustained hypertension. However, those children who are obese or who have hemodynamic manifestations of increased cardiac output (increased heart rate or systolic murmurs, or both) or who have one or more hypertensive parents are likely to carry a high risk of having sustained hypertension.[22,23]

3. Cigarette smoking: Cigarette smoking is one of the major risk factors for accelerated atherosclerosis and a major environmental cause of cancer and chronic obstructive lung disease. In addition, for the unborn, cigarette smoking by the mother has been shown to affect birth weight adversely. Cigarette smoking prevalence figures are estimates, because the data are based on varying definitions and self-reporting. Nevertheless, it appears that among adults, the proportion of men smoking cigarettes in the late 1970s was substantially less than that in 1964, whereas for women the reduction has been slight among whites and has not been seen at all among blacks.[24] It is clear that the habit begins early in life (ages 12 to 14) in substantial numbers and reaches epidemic proportions for teenagers aged 17 to 18 years. Again, a sizable downward trend for boys has been reported since 1970; for girls there was a steady rise in prevalence up to the mid 1970s, but a decline for all but the 17 and 18 year olds by 1979.[25–27] Thus the data indicate the possibility of progress in this area.

The reasons why American adolescents and teenagers smoke cigarettes have been studied intensively. It is known that when both parents or an older sibling smokes the child is much more likely to smoke. Success in academic studies and educational achievement are inversely related to smoking. Peer pressure has usually been cited as a major reason for smoking. The role of ubiquitous and persuasive advertising in the mass media cannot be assessed as an isolated influence but it has undoubtedly been a major factor in the decision to smoke.

The paradox in such widespread smoking by youth is the finding that the vast majority are aware of the dangers to health from smoking. Continued smoking under these circumstances suggests that conformity with group norms far outweighs fear of personal harm. Added to this are the risk-taking and defiance of adult standards so characteristic of some youth. Because it is apparent that many people smoke without immediate ill effect, the known dangers associated with smoking are not considered personally relevant to those adolescents and teenagers who start to smoke. There appears

to be a widespread delusion that youthful smokers have less difficulty quitting the habit.

B.. Risk Indicators

1. Obesity: Obesity has not been shown to be an independent health hazard in children; however, obesity is closely associated with hypertension, hyperlipidemia and diabetes mellitus in the adult. Overweight teenage college entrants are at greater risk of dying of coronary heart disease in middle age.[15] The obese child is at greater risk of becoming an obese adult, and thereby has a greater risk of having cardiovascular disease or diabetes mellitus, or both. Recent studies have shown a correlation between body mass and blood pressure in children and adolescents.[28–30] Many of these children and adolescents were obese. In addition, data from the Muscatine, Iowa study[21] and other investigations indicated that obesity plays a role in those children who have borderline hypertension on repeated measurement. Because of the association of obesity with hypertension, weight control is an important preventive measure in children. Finally, a recent conference held by the Nutrition Committee of the American Academy of Pediatrics concluded that obesity in a child had a profound psychosocial effect and recommended that preventive measures would have a beneficial effect.

The term *obesity* refers to an increase in body fat. *Overweight* refers to excess in body weight relative to standards for height. For most situations, overweight and obesity are used synonymously, although they are not identical. The clear definition of obesity is difficult because of the problems involved in measuring the contribution of fat to total body weight. Skinfold thickness has been used extensively to estimate the degree of obesity, but its value has not been adequately assessed through a wide range of obesity.[31] Until a practical method to measure total body fat is developed, a reasonable definition of obesity in a child is a relative weight (ratio of actual weight to expected weight for age, sex and height) of 120 percent or more plus a triceps skinfold thickness at or above the 90th percentile, or, in absence of skinfold measurement, visual assessment of the child as obese.

2. Physical inactivity: Physical inactivity is a risk indicator in children. The chance of obesity is increased and the sedentary habit may persist into adult years. There is no clear-cut evidence that exercise exerts an independent effect on prevention of coronary disease. However, regular exercise is to some degree associated with lean body mass and with a high level of HDL cholesterol. Also, although data are lacking, regular exercise may reduce tension and stress.

Perhaps most importantly, regular exercise promotes the concept of respect for one's body and reinforces efforts to eat a healthy diet, avoid the smoking habit, maintain physical fitness and avoid obesity.

III. Preventive Actions

A program directed toward preventing or retarding atherosclerosis, and risk factors for adult coronary heart disease and stroke, should include the following:

Identification and management of children with elevated serum lipids (Table I).

Identification and management of children with borderline and definite hypertension (Table II).

Identification and management of children with obesity (Table III).

Prevention of smoking.

TABLE I

Serum Cholesterol

Categorization	Action
Children with a family history of disease: 1. Hyperlipidemia 2. Premature cardiovascular disease 3. Hypertension	1. Measure total cholesterol × 3. If average at or above 95th percentile, measure lipoprotein fractions. 2. Measure total cholesterol in parents and their children. 3. Measure blood pressure in all. 4. Restrict saturated fat and cholesterol in diet. A. ≤300 mg cholesterol/day. B. 35% of total calories from fat/day. (1) 10% total calories: saturated fats. (2) *No more* than 10% calories: polyunsaturated fats. (3) Remainder monosaturated fats. 5. Discontinue oral contraceptives. 6. Reduce caloric intake if obesity present. 7. If no response to diet, refer for further evaluation.
Healthy children	1. Measure cholesterol levels only in those from high risk families. 2. Measure blood pressure levels annually and control obesity. 3. Healthy diet as above.

TABLE II

Blood Pressure

Criteria	Action
Definite hypertension (160/95 mm Hg × 3)	1. Staged medical evaluation. 2. Rule out secondary hypertension.[16]
Borderline hypertension (95th percentile or 140/90 ≤ 160/95 mm Hg × 3)	If still borderline: 1. Urinalysis and blood urea nitrogen determination. 2. Treat or prevent obesity. 3. Limit salt. 4. Discontinue alcohol. 5. Increase physical activity. 6. Discontinue oral contraceptives. 7. Continue evaluation and management.

TABLE III

Obesity

Criteria	Action
1. Greater than 120% of expected weight for height and age + 2. Skinfold thickness greater than the 90th percentile or visual estimate of obesity	1. Restrict calories to prevent excessive increase in body weight during growth period. 2. Restrict calories to reduce weight to normal after cessation of skeletal growth. 3. Develop habits to increase physical activity.

Development of the desire and habit to maintain a physically active life that will carry into adult years.

Development early in life of eating habits in the entire population that will promote a diet with adequate, but not excessive total calories, fat, cholesterol and salt.

The physician serving as a role model for good heart health habits for the child.

The physician serving as an advocate for health in the community.

A. Diet

Two of the major risk factors, hypercholesterolemia and hypertension, involve dietary intake. Until recently the main nutritional concern has been the issue of dietary adequacy. From the past emphasis on "adequate" or "balanced" diets there has been a shift to "prudent," "recommended" or "desirable" diets. It is no longer deemed appropriate to urge the public to eat more meat, dairy products, eggs, fruits, vegetables and cereal grains to obtain enough proteins, vitamins and minerals. There is new awareness that current mortality and morbidity in the United States are linked to a great extent to our dietary practices of *overconsumption* of specific foodstuffs. Thus, we are now concerned with the issue of maximal allowable (or desirable) levels of dietary intake as well as with minimal requirements.

Three dietary factors are currently known to be involved in coronary artery disease: These are (1) excessive intake of calories; (2) excessive intake of salt; and (3) excessive intake of saturated fats and cholesterol. The latter two factors often stem from the first. As a result, achieving proper caloric intake for an individual can begin to diminish excessive intake of saturated fats and cholesterol, and to lower intake of salt.

There are several approaches to estimating the optimal intake of calories for preventing obesity. The first approach is to rely on the current Recommended Daily Dietary Allowance standards (1980 revision).[32] These are:

Ages (yr)	Calories (kcal)
Boys and Girls	
1–3	1,300
4–6	1,700
7–10	2,400
Boys	
11–14	2,700
15–18	2,800
Girls	
11–14	2,200
15–18	2,100

Energy allowances for children (through age 18) are based on median energy intakes of children of these ages who were followed in longitudinal growth studies.[33]

Another approach is to propose that caloric recommendations for normal childhood populations should be related to the mean caloric intake of the different age groups:[33]

Mean Caloric Intakes (with standard deviations) by Age and Sex Groups

Age (yr)	Calories (kcal) Boys	Girls
1	1,332 ± 452	1,220 ± 406
2–3	1,555 ± 568	1,429 ± 555
4–5	1,851 ± 627	1,617 ± 524
6–7	2,082 ± 601	1,847 ± 619
8–9	2,222 ± 705	1,893 ± 601
10–11	2,317 ± 720	2,051 ± 771
12–14	2,607 ± 922	1,915 ± 699
15–17	3,097 ± 1,221	1,761 ± 699

These values are the mean caloric intake of white children in homes where income is above poverty level because black children and low income groups in the United States are leaner and, therefore, possibly undernourished.

These standards take into account neither amount of activity nor weight status (that is, whether under-or overweight). Thus, the standard may include too many calories for those who are relatively inactive and overweight and too few perhaps for those who are extremely active and underweight. Nevertheless, it is helpful to have guidelines for general recommendations of caloric needs of the different childhood age groups.

B. Dietary Fats and Cholesterol

As a guide, a diet for healthy children beyond infancy containing no more than 300 mg/day of cholesterol with 35 percent of the total calories derived from fat, less than 10 percent from saturated fat, about 15 percent from monounsaturated fat, and *no more than* 10 percent from polyunsaturated fat is safe and can be expected to result in lower serum cholesterol levels. To decrease dietary cholesterol intake as well as saturated fats, the child should eat less fatty meats, fat-containing dairy products and egg yolks. Healthy children with a serum cholesterol level of less than 160 mg/dl are unlikely to have a significant decrease in level when eating a low cholesterol, low saturated fat diet.[9]

It is important to remember that there are some childhood populations in the United States whose diet is not adequate in energy content and they may be inappropriately advised to follow such a nutritional practice.

Children with a family history of hyperlipidemia or premature cardiovascular disease have an increased risk of having hyperlipidemia.[7,11] Whether treatment for hyperlipidemia, other than diet, is indicated must be assessed individually. This depends in part on level of total serum cholesterol before dietary intervention and extent of response of serum cholesterol levels to the low cholesterol, low saturated fat diet. Use of the contraceptive pill is to be avoided when hyperlipidemia is present or when it develops with use of the pill.

C. Hypertension

As indicated, the prevention and correction of obesity in childhood and youth appear to have a great potential for reducing the level of blood pressure.

Numerous epidemiologic and animal model studies have shown that excessive dietary sodium is associated with an increased risk of hypertension, particularly for those with a genetic predisposition.[34,35] A reasonable recommendation is to limit the intake of salt to no more than 5 g (86 mEq sodium)/day. A diet of 5 g of salt/day could be achieved by eliminating most highly salted processed foods and sodium-containing condiments and by eliminating added salt at the table.

Given the several recent reports on the association between heavy intake of alcohol and high blood pressure, physicians have an added reason to do everything possible to prevent and correct the patterns of excessive alcohol use now all too common among youth.[36–39]

All children over the age of 3 years should have their blood pressure measured annually. In communities with children who are not seen regularly in a health care facility, physicians should assist in developing a system in which blood pressure measurement can be carried out. This is especially important in communities of black children, who are at particularly high risk of hypertension as adults.

D. Cigarette Smoking

Physicians and health care planners must build on positive motivations for achieving and maintaining optimal health. The role of the individual in accepting primary responsibility for his or her own good health must be one important basis for any anti-smoking program directed at youth. The physician must play a key role in supporting such an effort.

1. *Smoking in the doctor's office should be forbidden to all.*

2. *The physician should advise all patients beginning at an early age (perhaps 5 or 6 years) and repeated at each contact not to smoke.* This advice should be based primarily on positive aspects of maintaining optimal health rather than arousal of fear.

3. *Smoking habits of each patient should be elicited by the physician.* The physician should make every effort to persuade a child who smokes to stop.

4. *The physician should provide educational material related to smoking cessation.* Materials are available from the local American Heart Association, the local Lung Association, the National Cancer Institute (National Institutes of Health, Bethesda, Maryland 20205).

5. *The physician should refer smokers to cessation programs* and play an active role in the development of such resources.

6. *The physician must regularly monitor smoking habits of his patients,* taking advantage of recurrent desire on the part of recidivists to try again to quit. Unrelenting persuasion using all available techniques should be employed. The physician should never adopt a punitive, judgmental or defeatist attitude.

7. *For inner city unemployed youth,* the problem of drug abuse including cigarette smoking may not be dealt with successfully until underlying social problems are solved.

E. Exercise

Establishing the habit of regular exercise in childhood is appropriate and can lead to continuation of that good habit in adult life. Physicians and their families can serve as role models for the child and his family by engaging in regular exercise activity. They should include in a history a series of questions about exercise, including whether the child has entered the Presidential Award Program.

The physician should encourage exercise that the child will enjoy and is likely to continue through life, such as walking, climbing, social dancing, tennis, jogging, swimming, bicycling and cross-country skiing. Thus, the emphasis should be more on fun than on victory or record setting. Exercise is an important adjunct in the prevention and management of obesity.

F. Promoting Healthy Habits

The effective communication of health-related information from a busy physician to pediatric and adolescent patients and their families is one important aspect of the process of prevention of cardiovascular disease. This requires familiarity with basic educational techniques and a specific plan tailored to the particular needs of patients enrolled in a practice.[40–42]

The primary focus should be on those patients already motivated to acquire health-related information. The most challenging educational task is probably that of persuading the reluctant patient or family to seek information and help. Good listening and an enthusiastic approach at the outset of providing medical care can motivate even indolent, irresolute and hostile patients.

A variety of materials are available. The patient information booklet is the most common orientation method used by the physician.[42–45] The booklet should be targeted to the practice population's specific health beliefs and needs and should openly promote patient-doctor dialog. The physician's enthusiastic and brief oral overview of the booklet encourages its use and enhances the value of its content.

The most common method of patient education is one-to-one discussion. Although the use of this method best promotes the patient-doctor relation, it is better for reasons of time, energy and effectiveness to use an "educational prescription"—a mixture of educational modalities. This is particularly important for the patient being treated for a health hazard or risk factor, and should include written material to be read and taken home for others in the family to read, as well as referrals to appropriate agencies and programs.

Written materials are widely available, easy to distribute, economical, easy to update and can be distributed according to a tailor-made preventive care protocol. Thus, the obstetrician or family practice physician might establish a protocol to discuss family diet, smoking, and exercise habits, and to offer parenting advice, at a time when the prospective parents are most impressionable.

A variety of other methods can be used in the office: bulletin boards, posters, audiovisual programs, or even

patient libraries, depending on the characteristics of the practice.

Inherent in an effective educational program is good record-keeping to record the patient's progress within the suggested health maintenance education program or to assess compliance with a high risk protocol. Patient involvement is also enhanced by keeping a health maintenance record. The length of a patient's visit need not be extended. The repetitive nature of visits by children to their physicians allows constant reinforcement of good cardiovascular health habits.

The focus for preventive programs in Health Maintenance Organizations (HMO) remains to be sharpened. Physicians who work in such settings have a real opportunity to set up Cardiovascular Health Maintenance programs for the whole family. Implicit in the name HMO is the concept of preserving health, rather than sickness care. The promotion of preventive medicine makes good economic sense for society as a whole, but it is especially desirable in an HMO. Because the HMO utilizes the prepayment mechanism to finance medical care services, keeping the HMO member well will theoretically at least result in less utilization of resources and be financially advantageous to both providers and members.

3. School and Community Programs

It is important for physicians to be aware of the need to stimulate the development of health education programs outside their offices. These programs are aimed at the development and maintenance of good health habits and should be in place in the community school and college systems. Teaching large groups of children and young adults specific health education material pertaining to the acquisition and practice of optimal health habits should ideally take place through the curriculum in a sequential fashion from early grades through introductory college courses.

Because diet modification represents another major target of preventive intervention measures, physicians working in school and university medical care services should take every opportunity to help food services in these locations develop menus offering prudent diets and to educate students about them.

Physicians who work in school and university medical care services have access to students aged 17 through 21 years for whom risk assessment should be made and intervention initiated when appropriate. Their programs should provide blood pressure measurements for all students. They should identify adolescents and young adults with a family history of early death from cardiovascular disease, have serum cholesterol and lipoprotein determinations made, and do the same for young women in this group who are users of oral contraceptives.

Professional organizations whose cause is directed toward cardiovascular health have provided large amounts of educational material available to physicians and lay persons alike. The Americal Heart Association through its local chapters, the American College of Cardiology through its continuing medical education programs for physicians, the American Academy of Pediatrics through its Nutrition Committee and its newly formed Committee on Preventive Cardiology all serve as resources for the physician, the school and the community.

State governments are just beginning to approach the development of programs in prevention. The physician who plays a role in his own community's affairs should be in the forefront of support of programs that include cardiovascular health maintenance for children.

Finally, the physician who cares for children should let his Congressional representatives know of his support for the program in preventive cardiology mounted by the National Heart, Lung, and Blood Institute, which addresses in particular the training of physicians in Preventive Cardiology.

As the saying goes, "The child is father of the man." The child requires an advocate who aids him in the development of habits to maintain health, advocates wise programs to help in that mission and champions financial support for such programs.

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Task Force 2: The Physician in the Office (Adult Medicine)

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I. Basic Assumptions

The recommendations of this Task Force are based upon the following fundamental tenets:

A. The current extreme prevalence of patients with significant coronary heart disease and annual incidence of acute coronary events continue to constitute our major public health problem.

B. The cost of coronary disease in premature death (often sudden and unexpected), disability (acute and chronic), and in financial aspects (loss of earnings and cost of medical care) is enormous. The annual cost has been estimated to exceed $30 billion in the United States alone.

C. Current American medical practice devotes a disproportionate effort toward the treatment of disease once symptomatic, as compared with that expended toward its prevention. But this treatment effort is often too late, for many deaths are sudden and unexpected;

and once a major heart attack has occurred, the loss of cardiac tissue is irrevocable and impairs function even if death does not rapidly ensue.

D. Evidence indicates that major reductions in the rate of development of atherosclerosis and of the incidence and prevalence of its associated diseases—coronary heart disease, stroke and peripheral vascular disease—can be effected if major "risk factors" relating to its pathogenesis can be appropriately controlled or modified. The modifiable or controllable risk factors most urgently requiring intervention include: (1) smoking of cigarettes; (2) hypertension: at all stages and all levels; and (3) hyperlipidemia, especially hypercholesterolemia. Other related factors amenable to change include life style traits such as physical inactivity, obesity and heavy alcohol consumption. Moreover, the association between coronary heart disease and certain personality characteristics ("type A personality") appears to be sufficiently great to justify more careful monitoring of such persons with these traits.

E. Risk factor control and prevention of coronary heart disease are matters of major concern for government at all levels, as well as major medical, professional and voluntary health agencies.

F. Physicians in community practice have an enormous potential for further progress in solving this national problem. Many physicians have already become engaged in prevention and this trend may be one of the contributing factors in the decline of coronary mortality in the past decade. However, physicians can and should be motivated into more effective action for this potential to be fully realized for the welfare of the citizens of this country.

G. Major additional efforts should be made by the practicing physician, in coordination with other community resources and with the responsible participation of the individual patient, to control risk factors for atherosclerosis and coronary disease.

II. General Strategy

Two major problems relate to effective utilization of practicing physicians as an efficient force for the prevention of atherosclerosis. The first is the task of enlisting them into a significant expansion of their current efforts toward this still underdeveloped part of the practice of medicine. The second relates to the specifics of the physician's efforts, both in his office and in a community-wide campaign. The most important problem is obtaining the enthusiastic support of the physician for this undertaking. If physicians become convinced that effective prevention of atherosclerosis and coronary heart disease could be materially enhanced through their efforts aimed at optimal control of major risk factors, these resourceful and able practitioners could develop or seek out more efficient methods for the accomplishment of this goal.

It is more logical and efficient, however, for the methodology to be developed simultaneously so as to be immediately at hand when the physician becomes convinced of the need for such systems. This conversion of the potential energy of the physician into a highly efficient force for changing the destructive life style of Americans at high risk will require a major concerted national effort. At present, there is no general consensus among practicing physicians as to what should be taught to their patients and their communities, or how additional information can be utilized by the physician to control risk factors in the practice setting and community. Beginning this important definition is a fundamental goal of this Task Force.

III. The Enlistment of the Physician to a Commitment to a Program to Prevent Atherosclerosis and Coronary Heart Disease

A successful utilization of physicians in the attack upon the major risk factors for atherosclerosis requires that they be convinced of the effectiveness and feasibility of their more vigorous participation in this preventive effort. The most influential medical organizations and their leaders will be required to transmit to the individual physician the significance of the available data regarding risk factor control and the prevention of coronary disease; the inevitable conclusion must be that adequate care of their patients and families demands more effective control of these major risk factors. These efforts at physician education should be coordinated through all of the appropriate health professional organizations at their national and local levels. Federal health agencies should be actively involved in planning and implementation of these programs.

Coordinating Steering Committees: If such massive effort is to be successful, strong and adequately funded leadership must be provided. It is logical for the leadership of the American College of Cardiology and the American Heart Association to coordinate the development of a Steering Committee comprising representatives of appropriate health professional organizations and federal health agencies to implement the recommendations of this Bethesda Conference. This Steering Committee could develop a mechanism to seek financial support from private foundations and from the National Institutes of Health and other government agencies. Funding of this effort may well be obtained from multiple sources. The magnitude of the problem clearly warrants such an effort. This Task Force believes the challenge and opportunity offered by this project is worthy of an intense effort of the concerned voluntary and governmental national agencies.

The details of the organizational effort required to mobilize the physicians of this country are beyond the scope of this Task Force report; however, one attractive possibility envisions utilization of the state organizations of the most concerned professional organizations as a focal point for leadership in each state. A Steering Committee for each state appointed by the National Steering Committee could be responsible for establishing a comprehensive educational program involving each county of that state; Fellows of the American College of Cardiology and Fellows of the Council of Clinical Cardiology of the American Heart Association, among others, could provide expertise in program presentation. "Kick-off" meetings of all major county

medical societies could be carried out almost simultaneously. Major local media coverage should be actively sought, with interviews and telecasts coordinated by the Steering Committee in conjunction with the local affiliate staff of the American Heart Association. Audiovisual materials, including slides and videotapes with a carefully documented text, could be made available for scientific programs. Materials preparation should be the responsibility of the Steering Committee, possibly in conjunction with the Department of Health and Human Services or other governmental agencies. The initial meetings should be followed by programs throughout the year, with presentations to staff meetings of each major hospital.

IV. What the Physician Should Do

A. Risk factor screening and care: Physicians are motivated to do those things that they perceive to result in good health care. Simple risk factor screening is in the realm of almost all practicing physicians and should be considered an integral part of regular health care encounters. This should include: (1) a review of smoking and exercise habits, and an estimate of obesity; (2) a careful measurement of blood pressure; (3) measurement of cholesterol; and (4) measurement of serum glucose concentration. The findings of such screening should be systematically reviewed with the patient.

B. Assessment of probability of near-term coronary events: One important, yet easy additional step in the standard health care evaluation by physicians could be the systematic assessment of the probability of the patient's developing a near-term coronary event. The data required for this probability assessment include only age, sex, blood pressure, smoking history, determination of serum cholesterol and serum glucose concentration and an electrocardiogram. From these data and the tables included in the American Heart Association Handbook on Risk Factors, a probability estimate for the subsequent near-term development of an overt coronary event can be derived in a few moments without calculation or computation. The cost of obtaining this information is exceedingly small relative to its value—and to other medical costs. The great value of this estimate lies in the increased awareness of personal health care it creates in both the physician and the patient, and in the personal incentive it provides for the person so demonstrated to be at increased risk to attend to the major abnormalities detected.

C. Financial consideration for screening costs: Screening costs could be borne by the individual and should be made part of each new patient examination and general physical review at specified intervals. However, it is clear that if cost could be reduced, a greater public acceptance could be anticipated. The feasibility of developing financial incentives to encourage the patient to seek such screening should be carefully examined.

These incentives might include the following: (1) Direct deduction of a reasonable, standard cost of the Health Screening Examination from the taxable income, allowable by appropriate documentation. This documentation could be provided by the physician utilizing a standard reporting form similar to those utilized for insurance purposes. (2) Reduction of life insurance premiums upon receipt of documentation of such an examination, with further reduction if cigarettes are not smoked or smoking is abandoned, weight is kept at optimal levels, and hypertension or hyperlipidemia effectively treated if present. If all risk factors are optimal at examination, premiums could be reduced accordingly. (3) Health insurance policies could offer payment to the physician for such defined health screening on an outpatient basis at specified intervals.

D. The cost of effective risk factor intervention: The cost and recoverability of intervention efforts is a significant question that will require careful investigation. Many physicians do not have sufficient time for detailed counseling on smoking cessation, proper dietary habits, proper exercise, and so forth. In some cases, to achieve these goals, more office personnel, space and materials would be needed. It is recognized that all require funding above and beyond funds now committed for health care. In the short term, medical costs would rise. In time this expenditure should be recovered with interest as prevention of atherosclerosis begins to occur. As an alternative and complementary to this expansion of physician office capability, special community "Risk Factor Intervention Clinics" may be needed to aid physicians in this effort. These clinics could serve as referral facilities where patients could receive counseling on diet, smoking cessation, exercise training or other behavior modification, when such expertise, time and space are unavailable in the physician's own office. Clinical development, sponsorship and operation require careful thought; if done in proper consultation with the practicing physician, nonphysician clinics (possibly in hospital outpatient departments) staffed by appropriate health care professionals could function in an efficient manner.

Major carriers of health care insurance, including Medicare and Medicaid, should be strongly encouraged to provide special recognition of the importance of these efforts in preventive health care. It should prove to be both effective and economic for such recognition to take the form of payment for such outpatient services when carried out in a defined and standardized manner.

V. What the Physician Should Teach

This Bethesda Conference should initiate the most important national health care campaign for the 1980s and provide the basis for a major reduction in coronary heart disease, the nation's leading killer. This project should parallel the National High Blood Pressure Educational Program of 1970, but should surpass it in importance and comprehensiveness.

Despite great national and international scientific interest in the concept of risk factors for atherosclerosis, and considerable public interest and activity, there remains a lack of general understanding of these factors, their relationship to atherosclerosis and coronary heart disease and the fact that they are remediable. To an

important degree, this lack of sophistication extends to many members of the medical profession. To achieve the educational goals regarding coronary risk factors, simultaneous, coordinated campaigns aimed at all physicians (not only primary physicians) and other medical professionals, as well as at the general public, should be initiated, perhaps using as a model the National High Blood Pressure Educational Program. *The message, to be simply and clearly transmitted, includes:*

A. There is a continuing major national epidemic of atherosclerosis and coronary heart disease resulting in death or severe disability for millions of Americans each year.

B. In a great many persons, death or disability occurs prematurely during the "prime of life," and in a substantial number during youthful years.

C. There is convincing evidence that atherosclerosis has many predisposing features. Prominent are the five remediable risk factors: cigarette smoking, hypertension, high blood cholesterol, physical inactivity and obesity.

D. There is strong evidence that if these five risk factors are controlled by appropriate modification of life style, death and disability from coronary heart disease can be sharply reduced.

E. The individual citizen bears the responsibility for his or her own general health care regarding cessation of cigarette smoking, optimal exercise, weight control, proper diet (including appropriate attention to fat, cholesterol, sodium and calories) and the monitoring of blood pressure. This should be a "People's War" not a "Doctor's War" on coronary disease, although supported by all physicians in every way.

F. Medical responsibility includes educating the public (and patients) about risk factors and their control, and the development of systems for their efficient detection and control.

VI. Methods for Patient Education

Four broad strategies in this public health effort involve the individual physician in the office:

A. Physicians should be encouraged to examine their personal behavior and life style, to identify and control recognizable risk factors for coronary heart disease.

B. Physicians should recognize that they and their families are regarded by the community as role models in matters of health.

C. *Physicians should be encouraged to develop the office as an effective health teaching forum, setting an example for the community.* Office personnel should be instructed about risk factors and encouraged to control them. The waiting room should reflect the concern of the physician and the staff for sound health practices in appropriate posters, informational pamphlets and booklets, use of "Thank You For Not Smoking" signs, and absence of ashtrays. Material "personalized" by the individual physician and developed to meet the individual needs of his patients is most effective. For example, a videotape produced for national distribution, carefully planned for patients or lay groups, could be modified to include a "lead in" tape of the individual physician, communicating his commitment to the program content of the tape. The impact to that physician's patients and the probability of use by the physician would be increased. When possible, space should be set aside for patient instructional modules, where audiovisual materials can be utilized effectively: slide-sound shows, videotape or film cassettes, television tapes, anatomic displays or poster displays, pamphlets, and so forth.

D. *All physicians should be strongly encouraged to adopt a systematic periodic review of major risk factors with each patient as part of routine practice.* The results of this screening should be transmitted to the patient in such a manner as to educate as well as to inform. As described earlier in this report the determination of probability of early coronary events from the data obtained at screening is a powerful education tool. This effort might be facilitated by special worksheets and report forms designed for the physician's office.

E. *Development of a special physician's kit should be carefully investigated;* this might include a concise scientific review of risk factors for the physician and office staff; posters and pamphlets for waiting rooms and examining rooms; slides-and-sound for synchronized presentations; worksheets; report sheets; American Heart Association booklets such as one on risk factors, and so forth. Kits developed on a national level and made available at cost (or partial cost) to the physician, promoted by concerned professional groups including the American Medical Association, the various state medical societies, the American College of Cardiology, the American Heart Association, the American College of Physicians, the American Academy of Family Practice, the American Academy of Pediatrics and the American College of Chest Physicians, and others would enhance the uniformity of the message transmitted.

F. The basic concepts presented should be consistent with in-hospital teaching and general community educational messages.

G. *Development of "model teaching offices" in strategically located cities should be investigated.* These could serve as "field laboratories" to implement and evaluate teaching aids and strategies. They could be developed in conjunction with medical schools and teaching hospitals or by private physician groups; and they should be appropriately staffed and equipped to simulate the private physician's office. They should have space for patient education, with suitable audiovisual equipment and educational material development and/or in "field-testing" prepared materials. Careful follow-up should allow accurate documentation of the effectiveness of this model in risk intervention.

H. *Nonphysician Model Intervention Clinics* could be established in carefully chosen areas to identify patterns of use and to explore more fully the usefulness of this approach. Careful attention should be given to optimal interaction between the physicians of the

community, the hospital and paramedical personnel in the planning and supervision of these clinics.

VII. Recommendations

Recognizing the wide prevalence of coronary heart disease and the scientific rationale for decreasing its incidence by modification of key coronary risk factors, this Task Force recommends that an intensive effort be made to enlist the physician in an all-out national campaign in the 1980s to reduce these health hazards. In order to develop and implement this effort, and continuing the impetus generated by this Bethesda Conference, the leadership of the American College of Cardiology and the American Heart Association should organize a national Steering Committee including members from appropriate medical, professional, voluntary and governmental agencies to:

A. *Develop a detailed program on educating and enlisting the physician in risk factor modification.* This should include stimulation of state, county and local efforts to reach the physician.

B. *Help develop educational aids for the physician* to carry out patient risk factor reduction in the office.

C. *Develop a guide for the physician strategy in risk factor reduction in the office including:*

1. The personal role model of physician and his family.
2. The development of the physician's office and staff as additional role models (no smoking, for example).
3. The development of the physician's office as an education center.
4. Risk factor assessment as part of routine and periodic contact with patients.
5. The derivation of the probability of a near-term coronary event for selective patients for their education and enhancement of incentive for control of undesirable risk factors.
6. Utilization of community resources—nutritional guidance, quit-smoking clinics, hospital outpatient programs, weight control groups.

D. *Establish programs to develop and evaluate mechanism for financial support of this endeavor* and to evaluate the results of such risk factor intervention programs.

Task Force 3: The Physician in the Work Setting (Industrial/Occupational Medicine)

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I. Introduction

Coronary heart disease still accounts for more premature deaths than any other disease in the industrialized world. It is more humane, more economic and more practical to emphasize prevention of this disease than to try only to cure it.

The recent declines in deaths due to coronary and cardiovascular disease are generally believed to result to some degree from improved health behavior on the part of the public. Significant factors contributing to this phenomenon appear to be: (1) control of high blood pressure, (2) reduced cigarette smoking, (3) improved nutrition with resultant reduction in serum cholesterol levels, and (4) increased exercise. Other factors believed to have important value in controlling this disease include weight reduction, stress management and the modification of so-called coronary prone behavior.

This report assigns priorities to risk factor control based on an operational, best-judgment estimate of present-day ability to implement this effort in the workplace. Both the body of scientific evidence and the body of practical experience underlying these recommendations are bound to evolve, with resultant enrichment and refinement of goals and methods in the years ahead. Where scientific debate is current, approaches are proposed that are deemed sound, safe, feasible and useful, hence reasonable to pursue as components of this program. It is the goal of this Task Force to provide methods by which coronary heart disease may be reduced by implementation in the occupational setting of widely accepted preventive programs. The major goals are the establishment of health programs for all employees and suitable changes in the work environment.

The work setting should be seen as uniquely suitable or this disease prevention program. It provides direct ccess to a large number of people, currently some 90 illion workers. It offers the potential for reasonable ontinuing availability of the group, thus making pos- ble essential follow-up activities in ongoing pro- rams.

In the workplace, consideration must also be given o complementary activity related to exposure to po- ntially hazardous conditions that may have to be dealt ith as part of a preventive medicine program. These ıcludes stress, exposure to potentially hazardous ıbstances and other dangerous working conditions. It important that recognition be given to reducing and ventually eliminating from the workplace the haz- rdous substances and conditions known or believed to ontribute to the development of heart disease. These eed to be dealt with as part of a total program. Since ıey involve another set of considerations they are not ealt with in this presentation.

The workplace also makes possible the development f social support systems, through cooperation of labor nions, ethnic societies, social and recreational orga- izations that can help organize such programs, pro- ıote them and encourage continuing participation of orkers within them. Such programs also provide the otential for needed financial support through employer ayments, collective bargaining agreements or other ıutually agreed upon methods.

There are drawbacks to the workplace that should e identified and resolved. These include worker con- erns about the confidentiality of their medical records, rincipally because of possible threats to their job se- urity, and suspicion about the motivation of some mployer personnel or medical departments, or both, ı promoting such programs. Employers may resist ealth promotion programs because of potential costs. ı some medical communities there may be opposition y physicians because of perceived threats, whether real r imagined, to private practices.

A central question deals with why the work setting selected for special attention. In fact, the over- helming majority of physician-patient encounters ccur in the individual doctor's office. As important as ıese encounters are potentially for the preventive ef- ort (see report of Task Force 2), at least two facts in- icate the merit of emphasizing the role of the work- lace: (1) Large numbers of workers do not see their octors regularly except for the treatment of episodic lness; and (2) present reimbursement methods by third art payers usually do not cover preventive services.

Although the cost of such programs needs to be de- rmined, it is generally recognized that there is in- easing corporate interest in supporting and expanding ealth programs for employees. Health promotion ac- vities such as those outlined by this Task Force are med at the development of individual responsibility r health by participating employees and the en- ancement of the occupational setting as an adjunct to lving health problems and to health promotion. The ome also is an important occupational setting and may e reached through the employee in the work setting.

The demonstration of effective model programs is seen as having a potential ripple effect throughout American industry, and a potentially favorable economic impact due to the improved image of the workplace by the demonstrated concern of management for employees. The related incentives are independent of an immediate need to demonstrate cost effectiveness, reduced catastrophic illness and disability, reduced absenteeism, and so forth.

Role of the physician: The obvious assumption is that the physician has a role in the work setting in preventing coronary heart disease. It is also assumed that employees will benefit by the care and direction the physician can provide for the prevention of heart disease. This is true whether the action of the physician is direct or indirect through other health workers under his or her supervision. It is also recognized that the physician can influence institutional practices or the environment which may be contributing to the occurrence of heart disease. The goal of this report is to identify the most effective health promotion techniques for the prevention of coronary heart disease.

The increase in the cost of treatment argues for rational health promotion and disease prevention programs. Young employees come to the workplace with new and different goals and priorities, and with a higher level of social awareness. Concern for humanistic interest on the part of employers bodes well for enhanced work performance of employees who participate in such programs.

There are approximately 5 million work sites throughout the nation. Of these, about 14,000 work sites employ more than 500 workers. These account for approximately 25 percent of the 90 million civilian workers. The other 75 percent of workers are employed at plants with fewer than 500 workers. Of these, 85 percent employ fewer than 25 people. The importance of these statistics is that 2,500 physicians are employed full time in occupational medicine and nearly all of them work in plants that have more than 500 workers. About one fourth of these physicians are administrators, without direct responsibilities for patients. Another 10,000 physicians work part-time. Again, they are to be found mostly in settings employing more than 500 workers. There is rarely an occupational health service in plants employing fewer than 500 workers.

Any proposal for coronary prevention activities at the workplace must consider the diversity of the American occupational setting, the diversity of jobs in these settings, and the proposed delivery system most appropriate to the institution in question. To provide the most feasible solution for an occupational setting based on this report requires the establishment of priorities and methods for health promotion most appropriate to and feasible with the particular workplace.

II. Goals and Objectives

The goal of this Task Force is to point out the importance of the physician's role in the work setting and the manner in which his or her effectiveness can be increased in the prevention of coronary heart disease. The following goals and objectives are considered general

guides for individual programs outlined in later portions of this report. *The Health Promotion program should:*

1. Consider all levels of management, labor and health providers in the occupational setting, involving the spouse and family where possible. Recognize that work in the home setting is an occupation and that interest and adherence on the part of those in the home setting are important supports for the entire program.
2. Identify the specific disease prevention needs of participants.
3. Identify and define various types of participants.
4. Identify feasible models of health promotion in relation to those risks deemed important in the prevention of coronary heart disease.
5. Outline the roles of industry, physicians and employees and their organizations in the development and support of these programs.
6. Establish reasonable expectations for management, labor and physicians with regard to the success of this program.
7. Design and implement feasible programs.
8. Evaluate effects of programs for disease prevention.

Specific issues to be addressed include:

1. Definition of the proposed benefits.
2. Communication of the apparent benefits of the program.
3. Program administration.
4. Effective and efficient utilization of medical and health personnel.
5. Necessary equipment, facilities or services for the implementation of such a program.
6. Location, character and responsibilities of in-plant medicine.
7. Monitoring and controlling the adequacy of occupational medicine with regard to this program.
8. Motivation of health professionals to perform in accordance with the desired role.
9. Gaining the acceptance of workers for the health enhancement program and ensuring their continued participation, enthusiasm and adherence.
10. Education of employers and third party payers with regard to the importance of financing health promotion programs and services of this type at the worksite and in the community.
11. Increase productivity and diminish self-destructive behavior.
12. Determine the cost effectiveness and social benefits, while recognizing the focus on longer life with better health, that is, on the quality of life.

A. The Role of the Physician

As indicated earlier, physicians who provide medical care and health services for employees may be full-time or part-time workers or consultants. Such physicians respond to various needs of the population of workers within a great variety of occupational settings. Each setting has its unique goals and objectives. It is important that the health promotion program take into balanced consideration the need to develop a synergistic relationship between the goals and objectives of a corporation and those of its employees and occupational medical people.

The role of the physician is complex, involving the evaluation and implementation of scientific evidence as it emerges from careful and well controlled clinical trials, clinical investigations and basic research. The physician must promote the health of employees on the basis of current, scientifically valued medical and health information and must be convinced that the proposed program for education and intervention is important and effective. In the occupational setting, it is reasonable that activities for health promotion should be attempted that have the highest likelihood of visible success. Acceptance of health promotion is more likely if a small number of potentially valuable services be phased in rather than swept into existence. Each program should have careful monitoring and evaluation systems appropriate to its specific needs.

B. The Physician's Perspective

The physician's view of a program is that prevention of coronary artery disease presents an opportunity to decrease morbidity and mortality in specific groups of people. The opportunity for physicians goes beyond that purpose in several instances:

1. *Occupational physicians* are charged with advising employers on the maintenance of safe and healthful working conditions and performing health evaluations and on site health care, as well as other duties. The new dimension is that of health promotion, which incorporates an expanded educational role in addition to traditional health services.
2. *Public health physicians* may also be involved because of their concerns for regulations, public and professional education and administration of special health programs.
3. *Health maintenance organizations* may establish liaisons with business and industry and provide quality health care for populations at a reasonable cost.
4. *Family physicians* unrelated to full-time occupational settings are concerned with the health and morale of their individual patients.
5. *Biomedical scientists* studying the epidemiology, etiology, pathogenesis and treatment of heart disease and the rehabilitation of patients with disability from chronic coronary heart disease may become involved to elucidate opportunities and benefits for health promotion and disease prevention.
6. *Medical educators* may participate to teach principles of prevention and treatment and to provide clinical experience for students in the health professions.
7. *Cardiologists* participate to prevent cardiovascular disease and rehabilitate patients with coronary heart disease and other forms of cardiovascular disease.

All these illustrations identify the wide variety of physicians available for evaluation and implementation of the principles and programs espoused by the consensus of this conference. It is also important for phy-

sicians periodically to appraise and evaluate the success of a program.

Physicians will be aided by education in preventive cardiology. Components of the education should include: the data base for prevention of heart disease; epidemiology; program designs including organization, education and evaluation; technologic aides for retrieval of data; organization of resources; program implementation; evaluation.

Armed with the aforementioned abilities, physicians can have an important impact in: (1) public relations with participants; (2) professional relations with other physicians and health care professionals; (3) advocacy and persuasion; (4) technical services for early detection, diagnosis, treatment and rehabilitation; (5) expert knowledge; (6) educational resources; (7) appropriate referral; (8) designing, implementation and management of specific programs; and (9) research and evaluation of programs in order to provide industry and organized labor with a better sense of direction for program developments and cost effectiveness in coronary heart disease prevention.

C. Perceptions of Participants

It is important to realize that participants will need to know a considerable amount about the program in order to be motivated to participate. What are the presumed benefits? How do we best communicate the apparent benefits of the program and make it easily understood by the potential beneficiaries? How is the prevention program to be administered and conducted within the goals, objectives and functions of the occupational setting in question? As implemented, what is the role of physicians and allied health personnel? What is an effective follow-up mechanism to evaluate and communicate the impact and to make necessary modifications in the program?

Participants will be concerned about certain ethical medical practices and principles. Many of the programs will be educational in nature and do not involve the delivery of any form of medical or health care. In some areas, however, the programs will be prescriptive in nature. The programs will be voluntary and thus informed consent for the limits of the program will be a requirement in which the conditions and "risks" of participation are carefully spelled out. The possible distinction between the individual benefits and population benefits on the basis of control of risk factors also should be part of informed consent. Participants will be encouraged that the program entails no negative, unpleasant or harmful experiences or consequences beyond that of education and selective medical treatment as indicated. The program should be planned, conducted and evaluated by qualified experts in conjunction with representatives from labor and management. Again, it should be based on a clear understanding of the difference between conditions that are associated with or contribute to an illness and those that cause it.

III. Operational Perspectives

The remaining part of this report is divided into two main sections: Program Administration and Health Promotion Programs. The first section is designed to provide a framework in which a program can be administered in the work setting. The second section suggests specific health promotion programs that can be selected for use within the framework.

IV. Program Administration

A. Target Groups

To develop an effective employee health enhancement program, the cooperation and input of the following groups must be obtained: management, union management, medical staff and the employees (both wage and salary).

1. Management: The goals and objectives, potential benefits and evaluation systems have been outlined in the foregoing sections.

2. Medical staff: The medical department should be given responsibilities in the planning and in the implementation of the program. The large majority of employees will be asymptomatic with a wide range of indications for future health. It is to this group that the program must appeal since they will make lifestyle changes because of the value of the changes to them personally and not because they live in fear of becoming ill. Positive reinforcement is a strong motivational force.

Within any employee group, as outlined earlier, there will be a sizeable percentage of employees who demonstrate risk factors. These employees should be counseled and examined or referred for treatment, or both, by the medical director or his staff or by other local physicians. They should be motivated to change by the normal patient-physician relationship or be turned back to the general program to concentrate on individual lifestyle changes deemed most appropriate to reducing the risk factors identified in that patient by the physician.

3. Employees: Lifestyle changes cannot be legislated by management. Employees must understand the importance of lifestyle change and determine the importance of these changes to them personally. The planned program must create a sense of involvement and allow employees to make progress by their participation. Establishing mileposts and guidelines which can be achieved by participants is an additional powerful motivating force. The program must overcome the general employee feeling that "it won't happen to me." Statistics are a basis for predicting that it will happen to a predetermined percentage.

B. Strategy

The strategy for an effective employee health enhancement program requires three types of change.

1. Environmental change: Changes of the work environment that provide support to employees desiring to change their lifestyle as well as programs to eliminate

from the workplace those substances or circumstances likely to add to health hazards of exposed employees are of key importance. Improved food in the company cafeteria, fruit instead of junk food in vending machines, a place to exercise and shower, a smoking policy, promotional material, including a bulletin board to display current articles on health, are a few methods that have proved valuable in the experience of Johnson and Johnson, for example. These changes are highly visible to both managers and employees. They also serve as a constant reminder or feedback of the importance of lifestyle change. They also allow employees to watch the participation of other employees. In some cases, if the right employees get involved, a number of other employees will follow. This is an important educational technique referred to as modeling. Key individuals in management or labor may serve as motivational models by their actions which, indeed, speak louder than words.

2. Intrapersonal change: Individuals should begin by examining their own lifestyles and deciding on the changes that they personally believe need attention. Environmental changes will help support this effort.

3. Interpersonal: Because of the close association of employees in most work settings, there is a support function that occurs between employees trying to make similar lifestyle changes. Oftentimes they may jog together at lunch time or provide support to each other if they are trying to stop smoking or lose weight.

The synergism of these three types of activity in the work setting provides the opportunity to maximize lifestyle change among employees. Once this activity is well under way, an attempt to institutionalize the activity should be made. Plans for next year' program should coordinate with the company's cycle: planning, budgeting, implementing and evaluating.

Strategically, the above described effort will gradually provide a program of primary prevention. Secondary prevention should be practiced for those employees who have major cardiovascular illnesses and are returning to the workplace.

C. Program Criteria

The above strategy puts heavy emphasis on creating support systems within the workplace to aid in individual lifestyle change. To implement this program effectively, the following criteria are of value. The program should be:

1. *Voluntary:* There is no need for management pressure, but management participation is essential.
2. *Based on sound scientific and medical data.*
3. *Designed to provide freedom of choice programs.*
4. *Sustained over time rather than brief campaign activity,* that is, sustained follow-up for sustained participation.
5. *Focused on health enhancement and improved quality of life* rather than diagnostically oriented; it should not use scare tactics or blame as a motivator; positive reinforcement is more powerful.
6. *Evaluated at intervals for measurable results.*
7. *Flexible and adaptable to individual differences* and special *needs* for certain work units.
8. *Cost effective* over the long term.
9. *Evaluated with follow-up* of workers needing additional diagnosis or therapy, or both.

D. Health Screening

The measurement of an individual's lifestyle and biometrics through health screening provides an opportunity both to educate and to motivate the employee to lifestyle change.

1. Personal questionnaire: A large amount of information to help employees change lifestyle is available for the asking. A questionnaire covering medical history and personal habits (smoking, drinking, exercise, stress and nutrition practices) provides an excellent starting point.

This information should be collected confidentially. It is important for the employee to know that this information is for his value and no one else. If this confidence is violated, participation in the program will probably decline. The collection of this information will force the employee to think about health habits more carefully.

2. Biometrics: A record of measurements such as height, weight, blood pressure (diastolic and systolic), cholesterol, high density lipoproteins, pulse rate, and so forth will provide a quick overview of the employee's health. During the time this information is being collected, employees should be educated about the meaning of each measurement. Review of health habits from the questionnaire and of the biometric data provides the necessary information to analyze each participant and identify indications for future health.

3. Employee feedback: This analysis should be returned in a confidential manner to the employee. Areas for improvement should be suggested to the employee. This information will clearly indicate what needs to be done. Employees must be assured that the information obtained from such studies will not be used to jeopardize the job, seniority or opportunities for advancement.

Employees should be encouraged to seek advice about this feedback from the medical director and his staff or their personal physicians. Community programs to stop smoking; promote exercise; improve nutrition to prevent or control hyperlipidemia, obesity, hypertension, diabetes and to reduce stress are available from a variety of sources. The same is true of preventing or controlling alcohol abuse. Employees should be encouraged to enroll in these programs where improvement is required.

4. Correction of defects: No screening program should be initiated in the absence of a program designed to correct or adequately treat reported defects.

E. Evaluation

Summary tables of personal and biometric information for groups will provide an overview for the planning group with regard to the indications for health of all

participants. An analysis of this material will suggest those areas that are most in need of improvement.

Health screens that are conducted annually will provide comparisons with the previous year so that changes in the population can be determined. In a similar manner, if employees are given proper feedback, they will be able to determine the changes in both lifestyle and biometrics from their original health screen, as a group and—confidentially—as individuals.

An economic evaluation can be made by determining the changes in those factors outlined under the management section and then determining the value of those changes. As an example, if cigarette smoking was reduced by 30 percent during the year, a drop in absenteeism and in medical claims among the original smokers should be observed. The economic benefits of these changes should be computed. In a like manner, a group of employees who start exercising aerobically on a regular basis may find that they have less flu, upper respiratory infections and so forth during the year. In addition, there may be a reduction in the number of days away from work.

Based on the initial interest of employees in positive health programs, it may be possible to show that participants in the program have less turnover. If true, this would reduce hiring, training and separation expense.

F. Occupational Health and Safety

The above described activities should not be confused with the need or responsibility to improve safety and free the workplace of occupational health hazards. A medical director or consultant may assume this responsibility. The same person may be a logical advisor and supporter of the health enhancement program, including advising employees found to be at risk.

G. Summary

As outlined in the operational perspectives above, there is a substantial opportunity to reduce heart disease in the general public and at the same time to begin to counter the rapidly increasing cost of health care. The workplace presents one place to begin a health enhancement program. An annual health screening examination provides an opportunity to monitor progress of employees and to continue to motivate them. Once substantial numbers of employees have become involved, the effectiveness of the program will continue to increase. It can extend from a workplace to the home and from the home to the community. Over time, living healthy lifestyles should become a way of life.

V. Health Promotion Programs

Each of the individual programs for health enhancement can be envisioned under the supervision of a health enhancement advisory committee. The committee would be composed of key management, labor and medical personnel. The risk factors in coronary heart disease have been graded in priority for intervention on the basis of an operational estimate of present-day ability to influence them at the workplace. The American Heart Association and other community-based organizations can provide guidance and materials for the development of programs.

Priorities are ranked as follows:

A. Control of high blood pressure.

B. Reduction of cigarette smoking.

C. Improvement of nutrition for management and prevention of hyperlipidemia, overweight, high blood pressure and maturity-onset-diabetes.

D. Modification of coronary-prone behavior and stress management.

E. Increased exercise.

F. Control of alcohol abuse.

Each of these programs is discussed from the point of view of background, purpose, objectives, operating principles for implementation, services and evaluation.

A. Program: Control of High Blood Pressure

1. Background: A major national study sponsored by the National Heart, Lung, and Blood Institute in cooperation with the private sector has clearly indicated the value of identifying and controlling high blood pressure.[1,2] The impact of high blood pressure on a variety of cardiovascular diseases is indicated by the nearly 40 million Americans who have elevated blood pressure and the remarkable increase in risk that this condition creates in its uncontrolled form. Even minor or transient elevations of blood pressure are now identified as major contributors to coronary heart disease. Moreover, the means are now at hand to identify and control this most pervasive but assessable health risk.

2. Purpose: The purpose of this program is to reduce death and disability as a result of premature cardiovascular disease by the detection of high blood pressure in employees, by educating employees to the nature of high blood pressure and its management through pharmacological and nonpharmacological methods and by the continuing evaluation and reevaluation with individual counseling as deemed necessary and appropriate to individual cases.

3. Objective: The objective is to develop self-management potential through educating the individual by a variety of techniques. The incentive for control of high blood pressure is oriented toward delegating further authority for self-management to the hypertensive individual as that person demonstrates his or her ability for self-management.

4. Operational principles for implementation: Screening programs are well outlined by the National High Blood Pressure Education Program[3] and will not be discussed in this report. After initial screening or identification of the hypertensive person, it will be necessary to decide whether medical treatment will be provided by the corporation through the offices of its medical staff or by a private physician. At this point, the participant will enter the service portion of this program.

5. Services: It is strongly recommended that the participant receive an educational background through seminars conducted by health educators on an intramural or extramural basis. Intramural activities for

the control of high blood pressure are preferable. Educational materials, posters, reminders and individual counseling help to reinforce the importance of managing the disease that remains silent until a complication develops.

The pharmacologic management of the participant is best provided through the high blood pressure control guidelines under the principles of "Stepped Care".[4] Hypertensive participants can also benefit from nutritional counseling for weight control, salt restriction, avoidance of heavy drinking, and so forth. For the cigarette-smoking hypertensive person, there is increased risk and *smoking cessation* can be an additional benefit. Occasionally, the person with early hypertension will obtain value from exercise conditioning, and exercise may aid in weight control.

The program is organized as follows:

a. Identification of hypertensive patients will usually occur at the periodic physical examination. Baselines studies should include: (1) History and physical examination. (2) Chest X-ray film. (3) Electrocardiogram (12 lead). (4) Urinary analysis (microscopic). (5) Serum creatinine, potassium, cholesterol, uric acid and glucose determinations. (6) Assessment of additional risk factors that multiply the risk in the hypertensive person.

b. Consultations: To include the options available after outlining the degree of severity, extent of the problem and associated risks as well as the therapeutic goals of autonomy with self-management.

c. The options include: (1) The full in-house program implying both pharmacologic and nonpharmacologic components. (2) Total management by a private physician, outside health group, Health Maintenance Organization, public health group, or hospital outpatient service of the participant's choice. (3) Pharmacologic management by the local private physician, nonpharmacologic management by the corporate health promotion staff. (4) Medical management by the corporate health promotion staff without nonpharmacologic service. (5) No treatment.

For those who opt for any form of in-house managed pharmacologic therapy, the physician in charge must be highly sensitive to any perceived side effects that, by themselves, could diminish adherence. For those who opt for nonpharmacologic management within the employee health program, special attention will be paid to instruction and demonstrations in the following (where deemed appropriate): relaxation techniques; noncultist meditative techniques; nutritional counseling for sodium content of common foods; nutritional counseling for weight control where necessary; counseling for alcohol control where necessary; assertiveness training; exercise conditioning; and others as appropriate. The above functions should include the spouse where appropriate.

d. Failures: For those whose hypertension is not controlled despite adequate pharmacologic attempts, further investigative studies such as X-ray urography should be considered among other possibilities. When nonadherence appears to be the reason for control failure, special counseling and behavioral modification methods may be of value.

e. Incentive: For those who achieve autonomous control as defined by periodic checkups, a special incentive might be offered. This could consist of a high-level health awareness, promotion and stress management program provided to the successful patient and spouse at a retreat-like location.

The program might include: (1) Lectures on key subjects related to improved coping mechanisms, leisure activities (use and abuse), sexual problems, family problems, advanced nutrition and so forth. (2) Workshops or lecture topics for small groups. (3) Food preparation demonstrations. (4) Exercise and leisure counseling. (5) Free time. (6) Entertainment. It is anticipated that proper information in the hands of employees and spouses will serve as feedback to the company and to motivate other employees.

6. Evaluation: In hypertension, the risk is well accepted and well known. The effectiveness of therapy is easily measured by simple checkups and the effectiveness of the different therapy groups can also be assessed. Evaluation of the control of hypertension is a reasonably straightforward process requiring minimal equipment (blood pressure cuff) and can be part of routine evaluation by allied health personnel.

B. Program: Smoking Cessation

1. Background: The influence of cigarette smoking is one which directly relates the number of cigarettes to the incidence of coronary heart disease and sudden death.[5–8] In addition, there is strong evidence to support the influence of cigarette smoking in carcinoma of the lung as well as in chronic lung disease such as emphysema, bronchitis, bronchiectasis, high incidence of upper respiratory infection, and so on. Little question exists with regard to the value of cessation of cigarette smoking.

There are numerous smoking cessation programs available to industries from community, public and private organizations. The specific set of employee needs of each work setting will determine the type of program chosen. For purposes of this report, a cessation program that uses cognitive and behavioral methods is discussed. Aversive techniques are not included, although they are available from community resources. There has been much debate as to whether smoking is a habit or an addiction. The program described here deals with smoking as a behavioral problem, that is, breaking habit patterns rather than a pathophysiologic addiction to nicotine.

2. Purpose: The purpose is through a variety of techniques to reduce the number of employees who smoke cigarettes.

3. Objective: By reducing the number of cigarettes smoked and the number of smokers, to reduce the incidence of diseases of the heart and blood vessels as well as those of the lungs, including cancer of the lung, upper respiratory infections and chronic lung diseases. In addition, there are some "fallout" benefits such as reduced hostility between smokers and nonsmokers.

4. Operational principles for implementation: One cannot underestimate the potential effect some of the more practical factors have on the success of smoking cessation programs. If at all possible, the program should be offered to both employees and their dependents. Ideally, programs should be held for small groups of 8 to 15 people with one or two leaders. The room should offer a comfortable environment, be well ventilated and arranged in a manner conducive to discussion and sharing.

Sessions should be conducted before or after hours or during lunch hours. This is consistent with the voluntary aspects of the program and tends to demonstrate an attempt on the part of the employee to change behavior. As an added support, the employer should consider a no-smoking policy in certain areas of the premises. This policy may include the removal of cigarette machines from the work setting.

Smoking cessation is a very complex behavioral program. Most programs run for 6 to 8 weeks, meeting once a week for 1 to 2 hours. The advantage of weekly sessions is that employees have the opportunity to practice a new learned behavior while gradually withdrawing from their smoking habit. Six weeks is a minimal time frame for the actual program content to be provided. Of equal importance is the provision of reinforcement for 6 to 12 months after the program, with particular emphasis on the first 3 months. The methodology of this reinforcement is described in a later section.

Publicity for a smoking cessation program can be done by traditional methods of fliers, posters and desk drops. However, the most successful methods are those that utilize well established channels of opinion, such as labor organizations, employee leaders, regularly scheduled safety meetings or that elicit the support of management at varying levels.

Staff for the smoking cessation program should be recruited from the existing health personnel of the industry. This not only facilitates regular repetition of the programs but also provides continuity with employees over time. When professional resources are not available internally, contracts with local, public and private organizations can be arranged. Another possibility is to have employees who are ex-smokers conduct the program.

The professional resources are the basic support system for the smoking cessation programs. They should be either self-trained or have received some outside training. Training requires both reading, discussion and practice. Several of the references listed at the end of this paper are of value in self-training.[9–11] Community agencies such as the American Cancer Society also offer training. Ideally, the leaders should be ex-smokers; however, persons who have never smoked can successfully conduct programs. The presence of the smoking habit among health professionals continues to be a real barrier to the initiation of these programs.[12] One cannot underestimate the importance of a good role model.

There are several teaching techniques available for use in smoking cessation programs. Most programs are set up as group efforts to reach the maximal number of employees (and dependents). Groups provide the additional opportunity for participants to share experiences and effectively use peer pressure and support to reinforce new habit patterns. For each group member to have the opportunity to speak, the size should be kept small and coincide with the allowed time frame.[12]

5. Services: There are basically three types of teaching methods used in smoking cessation programs: cognitive, behavioral and aversive. The first method, cognitive, requires the employees individually to identify why they started smoking, why they currently smoke, what is pleasurable and distasteful about the habit, and/or why they want and do not want to stop. This is accomplished through list-making and discussion. The detrimental health aspects are sometimes discussed, but in general the population is well versed in this line of reasoning. Written and audiovisual resources may be used to stimulate or reinforce the discussion.[12]

The next step in the cessation process is to identify patterns in the individual's smoking habits. This usually is accomplished through daily record-keeping practice. The employee records some or all of the following: the time, place, mood, what was being done or with whom, the level of the need,[9] urge[10] or craving[11] to smoke. This latter recording is usually a rating scale of 1 to 3 or 1 to 5. The discussion then focuses on the behavioral patterns that are illustrated in this record and how the participant can begin to change these patterns by substituting a response that does not include smoking. In some programs, the change is oriented more toward problem solving,[10] in others toward a disruption of the habit sequence.[11]

At this point, the behavioral aspects of the program become more prominent. The scientific theory behind changing behavioral patterns is that the participant must learn to recognize and control through practice/repetition: (a) the stimuli or cues that trigger the behavior; (b) the response, smoking of a cigarette, or the urge; and (c) the reinforcement or consequences of this behavioral response. From this point on, the teaching methods focus on changing the stimulus-response-reinforcement pattern. Generally, behavioral programs focus on a gradual reduction in the number of cigarettes smoked, with a targeted quit date during the program. The behavioral patterns are changed in order to facilitate reduction.

The following list summarizes some of the more common behavioral techniques used to aid participants in this process[9–11]:

Changing brands.

Keeping a daily smoking record (attached to cigarette package).

Using a large jar to collect cigarette butts.

Not stockpiling, only buying one pack of cigarettes at a time.

Scattering smoking materials around the house.

Not carrying matches or a lighter, so one has to ask others.

Changing the hand used for smoking.

Putting cigarette down between puffs.

Keeping a daily progress chart or graph.
Keeping a piggy bank for money saved.
Having ashtrays, house, clothes, teeth cleaned.
Throwing out extra cigarettes.
Written contract with friend, professional or group.

Probably the two most common methods used in reducing and quitting are not smoking in certain places (that is, the car, office, kitchen) and gradually eliminating cigarettes by starting with those that have the lowest rating of craving or need. There are other helpful adjuncts such as relaxation and mental imagery (positive and negative) which can be used. During each of the weeks when these behaviors are being changed, the emphasis of the group leader should be upon reinforcing and praising the positive achievements. Discussions of negative behavior or failure should not be emphasized, just accepted.[12]

During the new ex-smoker phase, it is important that the participants have one or more accessible persons for support, either a professional, friend or group. Group meetings, individual counseling sessions, phone call support, and so forth, are also successful if employed on a regular basis. Since most people resume smoking during the 1st month after quitting, programs that stop abruptly after 6 or 8 weeks will be less successful. Reinforcement should continue for a minimum of 3 to 6 months after the program.

6. Evaluation: Because of the proliferation of smoking cessation programs now offered to industry and their reported varying success rates, a sound evaluation is necessary to determine the success of a program.[12] For purposes of this discussion, evaluation is limited to self report through questionnaire administration. Blood or pulmonary testing are evaluative options but their additional cost must be carefully considered.

A suggested evaluation protocol would include the following items as a minimum: (1) A smoking history form should be given at the first session asking for information about the number of cigarettes smoked, number of years smoked, age, sex, job level, presence of smoking spouse (or significant other), previous attempts at cessation, and locations. (2) Follow-up questionnaires should be administered at 3, 6, 12, 18 and 24 month intervals to determine retention or change in habit. (3) Response ratios should not drop below 80 percent for any of the questionnaires. There are additional research questions which can be asked about attitudes, beliefs and dosage patterns, but the time burden on employees and professionals will increase.

The evaluation of a smoking cessation program should yield information about who is able to quit, problem areas in the program, the success rate, and possibly some cross comparisons among the many programs offered. The same protocol should be used for all the programs offered. The type of statistical analysis performed on the questionnaire data will vary according to each company's objectives. It is also advisable to determine the existing prevalence of smoking in the employee population before the initiation of cessation programs. The evaluation will then yield data on how close the industry is to eliminating this behavioral problem.

Smoking cessation programs are one of the most common health promotion components offered in the work setting. It is clear that this behavioral change yields positive health results. Over time, these programs should be of benefit not only to the individual but also to the company and its financial investment in its employees.

C. Program: Enhanced Nutrition and Weight Control

1. Background: Good nutrition has long been recognized as an important component in the maintenance of health and the prevention of disease. Malnutrition, both undernutrition and overnutrition, can contribute in various ways to disease processes. While the relationship between nutrition and cardiovascular disease is as yet not fully clear, some moderation in dietary intake seems warranted. Moderation in intake of certain foods high in calories, fat and salt is appropriate until direct cause and effect relationships in humans are determined.

Dietary Guidelines for Americans, published by the U.S. Department of Agriculture and the U.S. Department of Health, Education and Welfare, recommend eating a variety of foods, maintaining ideal weight, avoiding too much fat, saturated fat and cholesterol, eating foods with adequate starch and fiber, avoiding too much sugar, avoiding too much sodium, and consuming alcohol only in moderation.[13] The *Surgeon General's Report on Health Promotion and Disease Prevention* specifies sufficient calories to meet body needs and to maintain desirable weight with reduction in calories if overweight, less saturated fats and cholesterol, less salt, less refined and processed sugar, relatively more complex carbohydrates from whole grain products, cereals, fruits, and vegetables, and relatively more fish, poultry, legumes and less red meat.[14] Although recommendations of official organizations are indefinite, evidence converges towards the conclusion that altering diet, particularly for individuals with elevated serum cholesterol levels, may delay the progression of coronary arteriosclerosis. The strength, consistency and plausibility of this argument suggest that the aforementioned recommendations are sensible and safe.

Experience tells us that for many the immediate pleasures of eating are little affected by remote possibilities of coronary heart disease. Since final proof is not available concerning the benefits of healthful diets, we must balance costs, risk, benefits and effectiveness for each recommendation. There is also a responsibility to provide individuals with the facts they need to make intelligent choices and to present a balanced view of the issues.

2. Purpose: The purpose of the nutrition program is to foster and encourage better quality dietary intake and the development of new eating habits including moderate intakes of fat, calories, sugar, salt and alcohol, and optimal intake of all essential nutrients (vitamins, minerals, calories, and so forth).

3. Objective: A better quality dietary intake will aid

individuals in maintaining health and preventing disease.

4. Operational principles for implementation: The likelihood that a nutrition program will be successful and the measures for quantitating its success depend upon thorough evaluation of employees and the occupational setting before the program begins. Demographic characteristics should be determined, health and illness data assembled, and summaries of health care service utilization should be prepared. Any physical and laboratory data relevant to nutrition and coronary heart disease should be sought. The history of nutrition programs and other health promotion programs presently or previously in operation should be reviewed. If possible, the attitudes of decision makers, middle managers, white collar and blue collar employees to health promotion programs in general and nutrition programs in particular should be determined. Areas that must be addressed in a nutrition program include attitudes, knowledge and skills of participants; patterns of cafeteria food choices; and food purchasing patterns in local stores.

Many avenues are available for establishing visibility and spreading information for a nutrition program. Newsletters, posters, mailers, lectures and demonstration, special food service menus and food displays all can be useful. The opportunity to develop social and environmental situations favorable for nutrition programs should be sought through targeting of specific operational divisions for intensive efforts in promotion and recruitment.

A special concern for promotion and recruitment in any nutrition program is involvement of other members of families, especially the wives of male employees. Diet and eating habits are very much family concerns and food preparation usually is in the hands of wives of male employees. Women employees who prepare food for their own families also need the cooperation of their husbands. More than in any other health promotion program, involvement of families in nutrition is particularly important.

Efforts at the promotion of nutrition programs must be sustained over time. Success is likely to be proportional to the resources available for continuing promotion, developing visibility and establishing credibility. Publicity for case reports and success stories in weight control, testimonials concerning perceived benefits, displays of group benefits in reducing weight and lowering lipid and blood pressure levels, establishing awards and prizes for weight loss, and publishing health care utilization data all are important in maintaining momentum for a nutrition program. The greater the visibility and enthusiasm for a nutrition program the more success is likely.

5. Services: Nutrition education should take as many forms as possible. Families of employees must be involved whenever changes in eating habits are recommended. Printed materials and audiovisual materials can be made available to individuals and groups. Lectures, demonstrations and discussions with small groups on a regular basis concerning food purchase, food preparation and eating habits are the usual approach to establishing cohesive groups. Personal counseling by a registered dietitian can provide intensive efforts directed toward individuals of special concern. A basic education in nutrition is no guarantee for establishing sensible diets and eating habits, but it gives participants the information necessary for making sound nutritional decisions. Topics on nutrition and health usually include information concerning constituents of diets such as caloric requirements for carbohydrates, proteins and fats as well as information on amount and sources of sodium, potassium, vitamins, and other trace elements. Practical guidelines for food preparation and food purchase also are useful.

Other relevant subjects for a nutrition educational program include behavioral factors. Objectives for diets and eating habits should be explained and specific actions described. The importance of stimulus control, eating habits and social influences should be emphasized. If contracts and incentives are to be used, their rationale and application should be explained thoroughly. Participants and health professionals must be concerned with issues of adherence to recommendations and maintenance of sensible diets and eating habits.

An important part of behavioral management is establishing specific objectives. Objectives should be established by each individual and objectives also should be established for the program. Objectives for individuals should cover food selections that have fewer calories, less fat, less salt, and more essential nutrients. These items should be readily identifiable to facilitate decision making. Vending machine food choices should also include a variety of foods including items low in calories, fat and salt. Many vending operations already offer fresh fruits and low fat or skim milk as alternatives to the higher calorie, higher fat items.

The issue of incentives should be considered when planning a nutrition program. In general, cost-sharing and time-sharing plans that involve use of company time and facilities for lectures, meetings and group activities should be matched by a commitment of time and expense by employees. Tangible rewards may be offered that have dollar value for reaching specific objectives but symbolic rewards that have token value but high visibility also can be good incentives. Prizes, award ceremonies and social events may provide symbolic rewards. The strongest incentives of all are peer approval and supervisor approval. Personal satisfaction in improved appearance following weight reduction also has incentive value.

6. Evaluation: The impact of a nutrition program on coronary heart disease would take several years to evaluate. Fortunately, the effectiveness of a nutrition program can be evaluated using other measures. Comparisons of participants in a nutrition program should be made with control groups that are properly matched or comparisons with baseline measures of the same individuals can be made before and during the program. These outcome measures may include attainment of specific objectives, interest and participation by employees and their families, continuing levels of activity

in the nutrition program, as well as comparisons with other similar groups.

Periodic evaluations provide information on the impact of the program and provide information to participants about the effectiveness of their own individual efforts. Measures to be evaluated include body weight, serum lipid levels, blood pressure, contents of food and activity diaries, problem detection and solution, health care utilization, measures of mood and morale, assessments of activities of daily living, and evaluations of job performance such as absenteeism, accidents, sickness and productivity measures. Analysis of these data should provide a basis for improving the program for each individual and assessing the impact on health, morale and job performance.

D. Program: Stress Management

1. **Background:** A recent poll revealed that 85 percent of Americans feel there is "too much stress in their lives." Although the definition of stress is not yet uniform, the perception of its effect appears to be well understood by the public. It is estimated that stress in the workplace and its effect on performance, absenteeism, alcoholism and disease costs American industry $10 to $20 billion per year.

Recently, a select committee of experts met with key officials of the National Heart, Lung, and Blood Institute to determine the role of coronary-prone behavior in coronary heart disease. The consensus of this group of 50 scientists was that type A behavior, as described by Rosenman and Friedman,[15] was a powerful factor in coronary heart disease and was deserving of equal rank with other risk factors.

There is preliminary evidence that the reduction of stress in industry is associated with: (a) an increased *esprit de corps,* (b) greater productivity (fewer mistakes), (c) a decrease in absenteeism, (d) improved employee/supervisor relations, and (e) a reduction in stress-linked illnesses. It is premature to determine the full impact of such programs and the validity of these preliminary impressions. It is not premature, however, to indicate that the stress management program is frequently viewed as the strongest indication of management concern for employees. Frequently these programs encourage employees to participate in other health promotion efforts offered by the corporation. As such, stress management is frequently considered the centerpiece of health promotion programs, although its formal relationship and established cost effectiveness remain to be defined over the next decade.

2. **Purpose:** To reduce the incidence of stress-linked illnesses in occupational settings through scientifically based stress management techniques and to reduce self-destructive behavioral patterns that may lead to illness and interpersonal job-related and other incompatibilities.

3. **Objective:** The objective is to make available the following types of programs for voluntary participation: (a) Cognitive reorganization (restructuring beliefs and attitudes); (b) assertiveness training; (c) relaxation techniques; (d) time management strategies; (e) modification of undesirable features of type A lifestyle; and (f) environmental restructuring to modify stress-inducing facets of the occupational workplace where possible.

4. **Operational principles for implementation:** It is important that such programs be directed by experienced professional personnel. Individual, group, seminar and clinical consultative experience is important. Involvement of the spouse is very helpful. Frequently, such programs can be moved from the occupational setting and conducted in the evening in order to obtain participation of the life companions of employees. In addition, the program must be in tune with the goals and objectives of the corporation. Management must understand that stress management needs to be oriented in a supportive fashion. At the same time, the perception of the participants must be that this is a program oriented primarily to the personal development of the employee. It is not a means of getting more work out of the employee. Successful implementation thus is based upon a clear mutual perspective between labor and management. In this area, behavioral psychologists may cooperate with the medical director in the program. Caution is recommended in selection of this type of personnel owing to the high sensitivity of the areas encompassed.

5. **Services:**

a. *Cognitive reorganization:* Unrewarding and self-defeating attitudes of individuals are unproductive and frequently self-destructive. Since this behavior is learned, it is optimistic to consider that it can be unlearned and that more suitable behaviors can replace the discarded, more destructive ones. This type of program involves new learning processes and therefore is strongly associated with the learning curve for memory retention. Whatever is accomplished within a period of 6 weeks must be reinforced for a period of time until it becomes incorporated in the individual's behavior. Group seminars are adequate for the majority of people; individual consultation may be required in selected instances. Individual structure will vary widely, depending upon the circumstances and the clinical instructor. Usually these courses are conducted for 2 to 3 hours twice weekly for 6 weeks followed by reinforcement sessions at intervals.

b. *Assertiveness training:* This type of program facilitates decision-making participation in working groups and the expression of thoughts and feelings in a direct nonpejorative fashion. Programs will be designed to examine supervisor-supervisee relationships, co-worker interactions, group participative activities, as well as training in conflict resolution skills and problem-solving strategies.

c. *Relaxation techniques:* Programs can be developed utilizing: (1) progressive muscle relaxation, (2) scientifically based meditative techniques, and (3) biofeedback-assisted relaxation. These techniques encourage employees to become aware of their levels of muscle tone in various situations and to develop countermeasures to the state of chronic physiologic arousal

deemed prodromal to many debilitating disorders (for example, high blood pressure, stroke, heart attack).

d. *Time management:* For many supervisors and managers, job responsibilities expand beyond apparent time available and a high stress situation with concomitant loss of effectiveness can occur when this becomes a chronic condition. This type of program can assist employees in analyzing and reorganizing current time expenditures to obtain maximal impact from this finite resource.

e. *Type A lifestyle modification:* It is important to recognize that approximately 50 percent of the male population in some studies and an increasing number of females demonstrate type A (coronary prone) behavior.[16,17] Some employees may seek assistance in modifying this behavior. Aiding certain employees in evaluating their overall effectiveness while competitive, aggressive and time-urgent offers initial awareness in setting the stage for behavioral change. When awareness has been achieved and recognition of potential health consequences of this behavior determined, the individual may recognize the increasingly ineffectual, self-defeating and perhaps even self-destructive nature of this behavior. Such awareness may provide the motivation to participate in one of the other stress management programs in an attempt to modify facets of this behavior. Individuals can be encouraged to experiment with alternative, less health-detrimental approaches to their work and leisure activities through the programs outlined above.

f. *Environmental modification:* Modification of stress-inducing facets of the workplace is powerful and important in stress management. These stressors range from subsonic vibrations that produce fatigue and irritability and lead to errors and potential injuries, to disruptive scheduling changes related to work shift. These factors can frequently be modified to the advantage of the individual and management alike. Although there have been relatively few studies regarding stress management in the occupational setting, limited research to date has demonstrated reduction in absenteeism and other encouraging results.

Despite absence of hard data, one cannot deny the importance of public reception of this program. It is perhaps the most personally and humanistically oriented of all those offered. Other programs frequently have to do with a "takeaway" approach. This program is oriented toward individual enrichment and can serve to offset some of the "don't do's" of the other programs.

6. Evaluation: Objective evaluation of the impact of an isolated stress management program remains a dream and not a reality. The program interrelates as a catalyst with other programs and, as such, the enthusiasm for the health promotion program in the occupational setting is a reflection of the satisfaction with the stress management program. Inevitably the impact on absenteeism, stress-linked illness and so forth can give a direction but is not a finite indicator of the program. Initially, one can utilize the "happiness index" on the basis of subjective questionnaires at the completion of the stress management program. Several psychological measuring sticks are available at this time. Utilization of such instruments will depend upon the type of program and the program director's background in stress management.

E. Program: Exercise

1. Background: Physical activity programs in occupational settings are increasingly popular as a means to promote the health of some employees. An explanation for their popularity may be that they offer a positive approach to cardiovascular health. Exercise is something participants can do for themselves in addition to what they enjoy already, whereas reducing weight, stopping smoking and taking antihypertensive medication seem, by comparison, to be inhibiting and unattractive. A convenient strategy for introducing health promotion programs may be to initiate an exercise program that incorporates group activities, divisional organization, leadership by volunteers and friendly rivalry among individuals and groups.

Although exercise programs have received a great deal of publicity, their benefits in reducing cardiovascular disease are still uncertain. Scientific evidence from many sources suggests that people who are vigorously active have less heart disease, have an increased sense of well being and are less depressed and anxious than are people who are sedentary.[18,19] If people entering an exercise program also stop smoking cigarettes, alter their diet, lower their body weight, reduce serum lipids and bring levels of arterial blood pressure to ideal values, then they probably lower their risk for cardiovascular disease. At present, it seems most sensible for physicians to advocate physical activity programs in industry as an adjunct to the elimination of cigarette smoking and to the control of blood pressure, serum lipid levels and obesity. The extent of discussion in this section is based upon the committee's consensus that the key issues involving the uncertainty should be presented.

The use of exercise tolerance testing in a physical activity program depends upon the intensity of physical activity to be undertaken and the risk for latent ischemic heart disease in participants. The value of exercise tolerance testing in screening individuals for strenuous exercise programs is not doubted. However, disagreement exists concerning the value of exercise tolerance testing in revealing the presence of latent ischemic heart disease in subjects without major cardiovascular risk factors. In persons under age 35 without manifestations of heart disease and without risk factors for coronary heart disease, exercise tolerance testing is not necessary in screening participants before they undertake vigorous exercise. However, exercise tolerance testing does provide a measure of cardiovascular functional capacity of an individual participant. Individuals over 35 and individuals with major risk factors for coronary heart disease should have exercise tolerance tests before undertaking a sizable increase in physicial activity. The

purpose of such testing during and after maximal or submaximal exercise is to detect electrocardiographic abnormalities indicating that strenuous exercise might precipitate clinical coronary artery disease.

2. Purpose: The purpose of advocating physical activity programs in industrial/occupational settings is possibly to delay or prevent the development of coronary disease. These programs may also serve as adjuncts to elimination of cigarette smoking and to control of blood pressure, serum lipid levels and obesity. They may serve to enhance physical work capacity.

3. Objectives: The objectives of this program are to reduce the incidence and prevalence of cardiovascular disease, increase physical fitness through participation in vigorous recreational activities, improve psychological health, reduce prevalence and severity of cardiovascular risk factors and avoid injury.

4. Operational principles for implementation: The likelihood that an exercise program will be successful and the measure for quantitating its success depend upon thorough evaluation of employees and the occupational setting before the program begins. Demographic characteristics should be determined, health and illness data assembled and summaries of health care service utilization should be prepared. Physical and laboratory data relevant to cardiovascular risk factors and coronary artery disease should be sought. The history of exercise programs and other health promotion programs currently or previously in operation should be reviewed. If possible, the attitudes of decision makers, middle managers and white collar and blue collar employees to exercise programs should be determined. Finally, a survey of community resources is useful to reveal what recreational facilities, physical fitness programs and physical educators are available. Also, the attitudes and knowledge of local physicians and the existence of similar programs in other settings should be determined.

Many avenues are available for establishing program visibility and spreading information. Newsletters, posters, mailers, lectures and demonstrations all can be useful. Specific individuals known to be at high risk for coronary artery disease or individuals of special concern to the organization such as decision makers and managers may be targeted for special effort in recruitment. An ideal opportunity to develop social and environmental situations favorable for exercise programs is the targeting of specific operational divisions for intensive efforts in promotion and recruitment.

A special concern for promotion and recruitment in exercise programs is involvement of other family members, especially spouses of employees. Recreational activities may take time away from the family and other family members may resent the loss of that time. If recreational activities can be shared, resentment may be lessened or avoided.

Persons with signs and symptoms suggestive of coronary artery disease, diabetes mellitus or other major medical illness should be encouraged to consult their personal physician.

An alternative to exercise testing as a preliminary step in obtaining clearance for vigorous exercise is to require a letter of permission to participate in an exercise program from the private physician of the prospective participant. This procedure shifts the burden of responsibility for safety away from the sponsoring corporation but it misses the opportunity to establish a baseline of cardiovascular functional capacity and to evaluate cardiovascular responses to a conditioning program. An intermediate step is to require a letter of permission from a physician for those individuals who are eligible to progress into a more advanced level of exercise.

Individualized exercise recommendations should be prepared whenever there is no contraindication to increased physical activity. The type, intensity, duration and frequency of exercise recommended should be based on the participant's health, estimated physical capabilities, physical activity interests and proficiency, and on the recreational facilities available. Guidelines to warm-up and cool-down periods as well as safeguards should also be specified for each participant.

Special attention should also be given to the manner of reporting results of health risk appraisals to personal physicians. A description of the program and its objectives, results of laboratory data obtained, physical measures made and other information available should be provided to physicians. Copies of reports given to the participants should be sent to their physicians, and a description of the programs available in the corporation sponsoring the health promotion and disease prevention program should be provided. Success of the program ultimately is influenced strongly by the attitudes of the physicians in the community; experience shows that they respond well when they are informed about programs involving their patients.

Many corporations have provided physical fitness facilities and hired physical educators to conduct programs. Community resources should also be utilized whenever possible to broaden the scope of programs by making facilities more accessible to families. Sponsoring programs limited to walking is excessively narrow; every effort should be made to include calisthenics, dancing, bicycling, swimming, racquet sports, as well as team sports such as volleyball, basketball and hockey. Even bowling and golf are a good beginning for sedentary individuals not accustomed to vigorous exercise. Use of community facilities can be monitored by attendance records and evidence of improvement in heart rate response to exercise, in strength and flexibility, body weight and skinfold thickness. As many facilities and professional personnel as possible should be available to all participants. Practical experience shows that if physical fitness facilities are to be used they must be close to work or home, pleasant and safe, and their use should be expedited by the sponsoring corporation on a cost-sharing and time-sharing basis with employees.

Corporations should also supply on-site facilities if at all possible. Showers and lockers for both men and

women are greatly appreciated by employees who walk, run or bicycle to and from work, and recreational facilities such as gymnasiums, running tracks, circuit training rooms, swimming pools and racquet courts are much more expensive than other resources for health promotion and disease prevention programs. Consequently, great care must be taken not to spend all the money available on elaborate facilities just because they are visible and fashionable. The purpose in establishing a physical activity program is to introduce other health promotion and disease prevention programs along with it. Therefore, enough resources must be available to develop a balanced program in addition to fitness and recreational facilities.

Good professional personnel supervising the health programs are even more important than good facilities. Those concerned with physical activity programs must be capable of much more than leading fitness classes and showing participants how to count their pulse rate. They also must be competent in nutrition, psychology and health education. Nurses, physicians, psychologists, dietitians and health educators also should be available as consultants. Employee volunteers are also valuable as leaders and organizers of employee groups. When these people are educated and supervised and their efforts channeled, they are an important source of spirit and enthusiasm for group recreational facilities.

5. Services: The components of a physical activity program include many services in addition to provision of recreational facilities:

a. *Baseline measures and evaluation:* Through these measures it should be possible to determine the health-related costs in a corporation, the epidemiology of health-related behaviors and measures, as well as the prospects for improving health and preventing disease.

b. *Health risk appraisal:* Present health status of employees can be determined and recommendations made to improve health and prevent disease. Detection of signs and symptoms caused by subclinical disease and referral for early care are valuable products of this service.

c. *Facilities:* These must be supervised, inspected, certified and maintained to ensure a high quality physical activity program.

d. *Professional personnel:* These individuals must be recruited, certified, trained and periodically evaluated to maintain a high quality program.

e. *Education:* Attention must be paid to improving attitudes, knowledge and skills of participants in exercise programs. Attention also must be paid to improving attitudes and knowledge of managers, decision makers, other employees and the general public in contact with program participants.

f. *Supervision:* Initial appraisal, individual counseling and periodic evaluation with feedback are essential parts of a physical activity program.

6. Evaluation: The impact of physical activity programs on coronary artery disease would take several years to evaluate. Fortunately, the effectiveness of health programs can be evaluated by using other measures. Comparisons of participants in a program should be made with comparison groups that are properly matched. Alternatively, comparisons with baseline measures of the same individuals can be made before and during the program. These measures may include:

a. *Outcome measures:*
   (1) Incidence of cardiovascular disease.
   (2) Physical fitness, including physical working capacity, body weight and utilization of facilities.
   (3) Psychological health, including psychometric tests, results of interviews and questionnaires and measures of satisfaction with work.
   (4) Cardiovascular risk factor prevalence and severity.
   (5) Participant satisfaction with physical activity programs.

b. *Economic benefits:*
   (1) Production costs, including absenteeism, productivity measures and employee turnover.
   (2) Health costs, including health care service utilization, accidents, medical illiness, insurance costs and insurance rebates.
   (3) Program costs computed on the basis of cost per participant and cost per employee eligible to participate.

c. *Social benefits:*
   (1) Employer-employee relations, including satisfaction with work.
   (2) Public relations including recognition from local government, general public, other corporations and customers.

F. Program: Control of Alcohol Abuse

1. Background: Alcohol abuse is in a different category from the other behaviors addressed in this report. Programs directed toward this problem are in the general realm of *treatment.* (There is of course a potential for progress in industry for the prevention of the occurrence of this problem; this area is dealt with in other reports.)

Unlike the health hazards of smoking, the health hazards of alcohol consumption relate almost entirely to its *excessive* use (either episodically or consistently) rather than its responsible moderate use. In addition to the well known mental and physical effects of alcohol, it is becoming increasingly clear that both hypertension and sudden cardiac death may also be related to its excessive consumption.[20–23] There is, of course, variable susceptibility to alcohol, but in general the threshold for involvement of heart muscle is between 3 and 6 ounces of alcohol/day (2 to 3 ounces of absolute alcohol). Involvement of the heart can occur on a variety of bases. Alcohol may induce abnormal heart rhythms. Alcohol has also been reported to remove components of heart muscle when taken in excess, and it is generally conceded that these are irreplaceable. The result is a loss of heart muscle that weakens the pump and may cause it to fail. In addition, the use of alcohol to excess deadens

the senses and may reduce angina, the signals coming from the heart that lacks oxygen. In this setting, an individual may perform more strenuous physical activity on the basis of the general "anesthesia" and the absence of a life-saving feedback signal.

Beyond the cardiovascular toll there is a well recognized individual and social toll that weighs heavily upon the effectiveness of any worker in industry and that worker's ability to maintain normal relationships in his home and community as well. Obviously, too, alcohol affects many other organs and contributes to a variety of diseases and derangements.[24]

2. Purpose: The purpose of this program is to identify those who utilize alcohol to excess and to control its use. Alcoholic injury to the liver is known to result from three or more alcoholic drinks per day (7 ounces of 86 proof or 3 ounces absolute alcohol).[25,26]

3. Objective: The objective of this program is to combat alcohol abuse through occupational or industrial medicine under the direction of physicians, to assure that no individual consumes more than 2 ounces of absolute alcohol/day if possible and to avoid increasing daily use of alcohol.[27–29] Early detection and rehabilitation are vital. Alcoholic rehabilitation programs should be designed to protect the employee's opportunity for work as long as the individual's work is satisfactory. Such programs utilized to combat alcohol abuse must also include public information on alcohol abuse that can be made available to all employees, their families and, when appropriate, to the community in general.

4. Operational principles for implementation:

a. *The health planning group and especially management and the union,* if present, must strongly and in an unqualified fashion commit themselves to support and implement the plan.

b. *The commitment and principles* must be spelled out specifically in an efficiently adopted statement of policy approved by management, labor and the medical staff.

c. *Funding* should be consistent to provide necessary staffing and operating expenses for the program.

d. *Alcohol abuse should be handled like any other disability* under the disability benefits program. Health and hospitalization insurance coverage might be extended to the same degree as for other medical or surgical diseases or disabilities; it might also include coverage of ambulatory and inpatient care. Currently, such an extension to facilities approved by medical departments is often available at no increase in premium costs.

e. *The program must be confidential* as are all medical matters.

f. *Employees can be referred* by themselves, a union steward, a supervisor or medical personnel as deemed necessary as part of the program.

g. *Supervisors should be given extensive training* in referral to these programs. New supervisory personnel should also be trained as they assume roles.

h. *Referral of workers by their supervisor* may be on the basis of defects in work performance not resolved by usual supervisory techniques. The worker should be told that the possibility of a health matter influencing work is the reason for the referral, not drinking or other reasons.

i. *Skilled professional counselors* should be available in the occupational setting to receive referrals, counsel and coordinate referrals to outside sources for ambulatory or inpatient care.

j. *Services of counselors in the health promotion program* should be made available to spouses or children of the employees upon request. Here the liability risk must be considered.

k. *Policy* should state specifically that involvement in the program will not be a reason for lower standards of work performance.

l. *The employee must be aware that continued failure to meet work standard requirements will require dismissal.* Action should be consistent with that notice after reasonable time has been allowed and opportunities made available for gaining and retaining control of health problems.

5. Services: In this instance, the services provided depend upon the resources of the occupational setting and those of the immediate community for providing alcohol control programs in line with the operational principles described.

6. Evaluation: Ongoing program evaluation includes periodic medical examination, employee work performance ratings by supervisors and absenteeism rates among others.

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Task Force 4: The Physician in the Hospital

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I. Introduction

Physicians, dietitians, nurses, hospital administrators and educators of Task Force 4 addressed their roles in the prevention of coronary heart disease in the hospital setting. The title of this Task Force Report indicates the physician's continuing primary responsibility in directing the present and future efforts to prevent coronary heart disease. These efforts must be directed not only at those with identified coronary heart disease and those identified to be at risk for future development of coronary heart disease but also at the entire population. This Task Force recognized early in its deliberations of this important health topic that attention had to be paid to formulating the total health team to provide important assistance to the physician so that the team effort necessary to provide the optimal educational impact can be accomplished. Therefore, this Task Force addressed the roles of all health professionals available in the hospital with regard to prevention of coronary heart disease.

The significance of the hospital as an industry and as a resource in the community was also considered. During the past 2 decades, the combined pressures of rapidly advancing technology and cost containment in the United States have forced hospitals to direct their resources increasingly to acute in-patient care. Hospital stays are becoming more and more complicated and briefer. A hospital stay is a confusing and emotionally stressful time for patients and their families. Under these conditions, where does prevention fit in and how could it become a more integral part of hospital services?

We recognize that prevention in the patient with clinical coronary heart disease encompasses far more than efforts directed toward risk factor modification. However, for the purpose of this document we shall be concerned with approaches toward lifestyle modification that can be universally applied to virtually all patients in the hospital setting as well as to the general community.

II. The Hospital's Role in Preventive Education

Although risk factor assessment, education and control should usually be instigated outside the hospital setting, the period of hospitalization is one in which the

potential impact of education is great and offers a unique opportunity for reinforcement. A patient's response to preventive education depends on three factors: (1) effective communication of the message, (2) the patient's intelligence, and (3) the patient's motivation. Patient motivation is significantly affected by changes in health status and, specifically, by hospitalization. Educational messages should also have an impact on asymptomatic ambulatory patients. However, this impact requires greater and continuing reinforcement, but ambulatory patients may be less anxious and confused than their hospitalized counterparts and therefore more receptive.

A. Cardiovascular Patients

Upon hospitalization, an individual's health becomes a central concern. The events that lead to hospitalization and the hospitalization period itself may be dramatic and frightening to the cardiovascular patient. The patient may have experienced episodes of angina pectoris or an acute myocardial infarction. In almost every instance, the hospitalized patient suddenly experiences heightened motivation to learn about risk factors and their prevention. In addition, the patient and family members are more available and likely to pay attention to the health education message.

In many hospitals, that have significant programs directed toward the diagnosis and treatment of coronary artery disease, preventive educational programs exist as well, but these programs are often haphazard and informally developed stepchildren to the diagnostic and surgical procedures. Physicians often do—but should not—limit their communications to the facts surrounding diagnosis and treatment. In institutions where cardiac patients, medical or surgical, are placed in designated nursing units, the circumstances for initiating educational programs are particularly favorable. The nursing staff often develops *instructional programs* for their convalescing patients. However, these educational activities commonly remain isolated, and the efforts cease at the time of discharge. There should be improved coordination of these efforts among nursing staff, physicians, and other professionals who might carry these activities into the postdischarge period.

B. Noncardiovascular Patients

The unmet potential for preventive education in the hospital setting is *not limited to the cardiovascular patient*. The hospital could provide all appropriate patients with important information on their coronary health status based on routinely performed tests. These results could be correlated with self-administered questionnaires or staff interviews on admission concerning the subjective and objective data relating to coronary heart disease (for example, tobacco use, blood pressure, lipid levels, weight). Such information developed in the patient's chart then becomes available for the attending physician's review and subsequent recommendation of an educational program during the stay in hospital or thereafter.

Before or at hospital discharge a specific *plan for follow-up* should be approved by the attending physician with notation as to what has been done and how further efforts will be pursued. Only the patient who has been well informed by health professionals in the hospital is properly equipped to assume responsibility for any necessary changes in lifestyle and preventive therapy (for hypertension, for example).

C. Linkages Between Inpatient and Outpatient Programs

Although many hospitals are involved in community health education, appropriate *linkages between inpatient and outpatient programs* have not been delineated. A continuous preventive program should be developed by physicians in collaboration with nurses, dietitians or other health professionals. *The following steps should be taken to develop or enhance existing ambulatory programs* in local communities to carry out continuing activities to reduce coronary artery disease and atherosclerotic disease in general:

1. *Standardized program guidelines* should be developed by a national joint committee of representatives of the various professional organizations concerned with prevention of coronary heart disease. These guidelines should be prudent and based upon established scientific facts utilizing, wherever possible, information from already established programs. The program guidelines should ultimately contain information on the risk factors related to coronary heart disease and on measures to alter or control lifestyle, including dietary and smoking instruction, exercise information and supervision (if an exercise facility is available) and information on control of high blood pressure.
2. *Local courses and counseling services,* based on the above standardized program guidelines, should be established or expanded.
3. *The means for continued financial support* should be assured from the outset to ensure the longevity and quality of the program.
4. *When such a program has been established, physicians should be encouraged to recommend participation* to their patients with cardiovascular problems, whether established or potential. This ambulatory program should be recommended either at the time of hospital discharge or at the time of identification of cardiovascular risk factors. Further outreach to the entire populace, or to specific segments—for example, school populations and members of civic organizations and labor forces—should be a continuing consideration by the educational program.
5. *The hospital should share sponsorship* of such education programs with its medical staff and other institutional health professionals.
6. *The hospital should supply resources*—both physical and public information—to support the growth and strength of this educational program.

III. The Hospital As an Employer

The hospital should be a model as an employer interested in the health and well-being of its employees. It should *provide programs* that survey, inform, guide and encourage the development of *positive health habits.*

The hospital should provide an assessment of health risks for all employees beyond the immediate demand for care of acute disability and worker compensation. There should be a nutrition service that provides education and food service consistent with the prudent diet to reduce risks of coronary heart disease. There should be programs to inform and aid in the control of weight and cigarette smoking. Each employee should be informed of his or her own blood pressure, serum cholesterol, weight and the adverse effects of cigarette smoking.

There should be employee health programs related to lifestyles and coronary risk factors. This exemplary role may take many forms—the regular provision of health awareness campaigns; establishing good health practices within the hospital facility such as enacting stringent smoking regulations for patients, staff and visitors; carefully noting on all menus for patients or visitors the nutritional content of the food served and identifying those selections that are particularly healthful; providing exercise and fitness programs. The health care forces in the hospital should cooperate to teach patients, employees and visitors that good health is a personal responsibility and each should know his or her status related to the risk factors of his or her age and sex.

IV. The Hospital As a Resource

The hospital and its staff should be a community resource in blood pressure screening, programming for cigarette smoking cessation, blood lipid screening, weight control, diagnosis and management of diabetes mellitus, exercise activity and cardiopulmonary resuscitation. In addition, hospitals have several unique opportunities to take a leadership role in education for prevention of coronary heart disease. They can provide a facility for activities such as community education, patient education, physical fitness classes, self-help and support groups and risk-screening programs. The community usually views its hospitals as institutions that are capable of organizing and activating other agencies in the local area. In addition to providing physical space for prevention services, hospitals frequently have ongoing working relationships with other agencies and institutions in the community and can draw upon their help to supplement the resources, including funding, needed for prevention activities.

Hospitals can influence the education of professionals who are obtaining their clinical experience in hospitals. The curriculum for medical, nursing, laboratory and other technical personnel should include a significant exposure to preventive cardiology. Staff education as well as continuing education conducted by the hospital for its employees should also emphasize preventive and rehabilitative services.

V. Health Professional Roles in Preventive Education

The hospital may be viewed as bricks, mortar and sophisticated equipment, but it is the various professionals within that physical structure who must work together to produce a program that successfully accomplishes the goals set forth by this Bethesda Conference. Four specific groups, present in all hospitals, were discussed by the Task Force: physicians, nurses, dietitians and hospital administrators.

A. Physicians

The advocacy role of physicians regarding behavioral change for the prevention of coronary heart disease cannot be overemphasized. Studies have shown that the physician is the person most likely to influence patient behavior in regard to health. If we are to improve preventive medical care in this country, we must convince physicians of the value of the preventive approach so that they will convince their patients.

In the hospital setting the leadership of the medical staff should encourage the continuing education of their colleagues in coronary risk prevention. Physicians should participate in committee and teaching functions for education of coronary risk prevention.

The medical staff must appreciate the need to utilize nursing, dietary and other professional support in developing strong coronary prevention programs. Physicians should assure that all patients are informed of all risk factors.

B. Nurses

Because of sustained contact with patients, nurses are in an ideal position to reinforce the patients' understanding of risk factors, to present portions of the educational program and to assist in preparing patients to assume the necessary responsibility for their own behavior. The role of the nurse is particularly significant in the early planning for discharge. Many nursing educational programs now prepare nurses for their important role in the prevention of coronary heart disease. However, nurses generally need to be encouraged to accept this involvement, by staff development programs and recognition of their responsibility.

C. Dietitians

Because the risk factors for coronary heart disease are significantly related to various aspects of nutrient intake, the dietitian should be actively involved in the health care team. This involvement should include assessment of the nutritional well-being of the patient and assistance in the practical application of physicians' diet prescriptions for patients and their families. Such dietary consultations should be available to hospitalized and ambulatory patients, as well as to participants in ambulatory programs to decrease the risk of coronary heart disease in asymptomatic individuals.

The dietitian should assure that the food service provides all hospitalized patients with a diet that is attractive and palatable and that reflects nutritional recommendations appropriate for risk reduction of coronary heart disease, that is, reduced calories from total fat, particularly saturated fat, decreased cholesterol, decreased sodium and reduced caloric intake where appropriate. Concurrently, this diet should emphasize the intake of foods that are high in complex carbohydrates, vitamins and minerals in relation to other nutrients. Although the brief period of hospital-

ization for most patients cannot be expected to lead to a long-term change in eating habits, it can provide a beginning for continuing education about dietary modification.

The dietitian should ensure that employee food service facilities in the hospital include diets that meet accepted recommendations to reduce risk of coronary heart disease.

D. Hospital Administrators

Hospital administrators should seek opportunities to implement effective programs for the prevention of coronary heart disease. After assessing the needs of their specific communities, administrators should determine the most appropriate method of fulfilling those needs, as an important objective of the hospital. Administrators should provide appropriate risk factor identification and education programs for all hospital employees and should adopt hospital policies and procedures that are in concert with known, effective preventive techniques such as prohibiting the sale of smoking materials and of smoking, except in designated areas, and providing food services that support nutritional standards. Wherever possible, hospital facilities, staff and teaching resources should be made available for prevention programs. Administration should actively seek funding sources to support prevention activities.

VI. Recommendations

A. *The physician in the hospital setting* has the responsibility to initiate and direct appropriate efforts to prevent coronary heart disease in both in- and outpatients, as well as the institutional staff and employees. Optimal discharge of this responsibility requires a team effort; key members of the team include nurses, dietitians and hospital administrators.

B. *Hospitalized patients should be given the information in the medical record* about their weight, blood pressure, blood sugar, serum cholesterol and other factors. Preventive recommendations by the attending physicians should be included in the discharge summary. Educational efforts provided by physicians, nurses, dietitians or other health professionals should be noted in the medical record.

C. *The hospital should offer a coronary risk assessment program* available to both in- and outpatients upon request of their physicians.

D. *The hospital should provide a program for its employees and staff* for risk factor assessment, including blood pressure, smoking pattern, serum cholesterol, body weight, diabetes mellitus, nutrition and physical activity. Health programs should be available to help employees and staff modify lifestyles and risk factors.

E. *The hospital should serve as a learning center that encourages coronary prevention in the curriculum of all students affiliated with it.* It should provide a health education program under the supervision of the medical, nursing and dietary staff for employees, patients and members of the community.

F. *Standardized educational program guidelines should be developed* based on prudent judgment and established scientific facts from which local ambulatory programs can be developed or existing programs enhanced. These programs, if sponsored by the hospital, should be under the supervision of health care professionals associated with the hospital. The hospital should look to its medical staff to provide guidance in these programs.

G. *A prudent diet should be available* and physicians should, when appropriate, encourage its use. This diet should be clearly identified for selection by hospitalized patients, employees and staff.

Task Force 5: The Preparation of Future Medical Practitioners (Medical Education at the Undergraduate, Graduate and Postgraduate Level)

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I. Introduction

The primary focus of the Task Force Report is the development of a meaningful and effective educational program for coronary prevention, with emphasis upon a curriculum that encompasses and integrates the education of medical students, house staff and practicing physicians. One cannot underestimate the importance and the problem of developing and implementing a curriculum on cardiovascular disease prevention. The report of this Task Force is designed to be of help to all who wish to advance this critical area.

Because of the continuing large incidence of coronary heart disease, the potential for prevention of premature morbidity and mortality is great. To realize this po-

TABLE I

Plan for Curriculum Development*

Needs Assessment	Content Outline	Specific Program Outline	Evaluation
1. Identify desired final knowledge, skills, attitudes 2. Clarify entry level of knowledge, skills, attitudes	Specify required program content to satisfy training needs ↓ Specific learning objectives	Specify appropriate learning modalities and develop syllabus and training materials ↓ Mediated programs Computer assisted software Patient simulations Problem solving exercises Appropriate visual aids	Learner 1. criteria setting 2. measurement of performance Program 1. Formative 2. Summative

* Evaluation involves all parts during—not after—development.

tential, medical students, house staff and practicing physicians should become familiar with the basic principles of epidemiology and the primary prevention of coronary heart disease.

Because many interventions for reversing risk factors, for primary and secondary prevention have at times been implemented before they have been definitely proved to be effective, each intervention should be categorized as unclear, possible, likely or of proved scientific benefit. For certain intervention approaches, reasonable differences of judgment may exist as to efficacy. Thus, an effective teaching program must consider this matter.

Significant reduction in coronary heart disease mortality has occurred during the last decade. However, data are limited and inconsistent as to whether a decline has occurred in the incidence of this disease, and in any case millions of people continue to be at risk for premature mortality and morbidity resulting from this malady. This stimulates a desire to broaden and improve our attempts to reduce these risks. For various reasons, a person highly effective in working with individual patients—the primary care physician—is often not formally involved in this effort.

To date, physicians have received little focused information in medical school about preventive cardiology. Epidemiologic, clinical and laboratory investigators have identified risk factors for coronary heart disease. The public and individual patients must be informed about them in a convincing manner. The busy days of practicing physicians are already filled with the needs of patients with acute problems, leaving little or no time properly to explain risk factors and to motivate individual patients to change their lifestyle. However, recent surveys indicate that people think they will be more inclined to alter their lifestyle on the recommendations of their physicians than on recommendations from any other source. For this reason practicing physicians must be trained to provide the latest information on risk factor control to their patients. Physicians must be encouraged to assume responsibility to make the information known to their patients and to monitor their adherence to the advice given.

The purpose of this Task Force on Preparation of Future Medical Practitioners for the prevention of coronary heart disease is to present specific plans to accomplish this on a large scale basis with the most efficient use of physicians' effort and time at the lowest cost.

Four issues are addressed by this Task Force. These are: (1) To design programs to teach prevention of coronary artery disease in such a way that the principles will become incorporated into the routine practice of medicine. (2) To assure that continuing medical education programs provide the most current information to the practitioner that will enable him to pass this on to his patients. (3) To develop a system of evaluation that will allow valid assessment of preventive measures in the management of patients from infancy through late adult life. (4) To develop strategies that will stimulate educational institutions, professional organizations and funding agencies to promote scientific concepts in research and other efforts in primary prevention.

The specific knowledge and skills that the practicing physician, the house staff and the medical student should each have in order to provide direct patient care, or to participate in relevant patient education programs are outlined.

II. A Plan for Program Development

Educational objectives of teaching programs for medical students, house staff and practicing physicians, developed by faculties in schools of medicine, are best accomplished by following an orderly structure of curriculum development, implementation, and evaluation. A useful approach is outlined in Table I. This table outlines a general approach to curricular development, relates this to the development of a program in prevention of coronary heart disease and provides a content outline for this development. Classically, the initial step is a needs assessment that identifies the skills, knowl-

edge and attitudes that should be required of physicians to perform their task in an optimal manner. The needs assessment is indispensable and is usually best accomplished when a group of experts with scientific knowledge and practical experience agree on the optimal behavior goals.

The next step is to define in clear and relatively specific terms the content of a training program that will yield the desired behaviors. The development of this content outline may be refined in a succeeding step by a statement of learning objectives that specify the desired behavior (see *Appendix 1*).

Several aspects of the content outline deserve comment. The outline is intended to be comprehensive and assumes that the entry level is that of a 1st year medical student. No previous knowledge of epidemiology is assumed; this content outline may be used to teach the principles of epidemiology. However, the content outline is not designed to be slavishly followed. Rather, it is intended as a guide or checklist. Moreover, it can be used to design postgraduate education programs as well.

On completion of a content outline (or specific learning objectives), specific curriculum approaches can be defined and developed. These approaches can and usually do encompass a variety of teaching modalities. In development of a specific curricular approach, it is important to match the teaching modality to the learning need. Conventional lectures, syllabus study and audiovisual programs can be developed for information transfer, but the learning of most skills requires actual interactions with case material. A variety of approaches is often required, and care should be taken to match the required behavioral change with an appropriate learning modality. Examples of programs that integrate different approaches include Advanced Cardiac Life Support, Preventive Cardiology Academic Awards and Summer Epidemiology Seminars. In the Advanced Cardiac Life Support program, a syllabus, lectures, problem-solving exercises, identification of arrhythmias and psychomotor skills in intubation and resuscitation comprise the teaching approaches.

An important and often neglected step in program development is evaluation, which includes learner assessment as well as program assessment; evaluation is discussed in section III of this report.

In undergraduate medical education, many topics in the outline are already covered in some schools. The intention is not to rearrange scheduled lectures or replace one topic with another. Rather, the content outline represents a checklist that can be used by faculty and curriculum committees for their integration of curricular coverage. In this manner, faculty can define and correct current deficiencies and ensure reinforcement of the concept throughout the curriculum. For example, many basic aspects of lipoprotein and lipid metabolism are presented in biochemistry. Nevertheless, the synthesis between biochemical aspects and clinical features, such as diet, exercise, diabetes and alcohol consumption, may not receive attention; this synthesis must be presented to the students, so that they see preventive cardiology as an integral part of patient care. Many other areas currently receive little attention and their inclusion in the outline should serve as a reminder of their importance. For example, patient adherence to modification of life patterns is fundamental in improving general health and is critically important in prevention of coronary heart disease. This topic is not usually specifically covered, and its importance is not widely appreciated in medical student training. The use of this content outline may influence curriculum designers to include training in these skills in the curriculum. Although the participants in this Task Force recognize that each medical school faculty is responsible for its own curriculum, it is hoped that the outline provided in this report will serve as a stimulus to reexamine and improve each school's efforts in preventive cardiology.

Although the content outline has been developed primarily for medical students, it can be used to define teaching programs for house staff and for continuing medical education. The requisite knowledge and skills are the same for all student groups. The process may change depending on differing practice situations, but the principles and the educational goals are not different, because the best patient care is the final goal.

III. Evaluation

First, the individual student must be evaluated in terms of his or her learning experience. This requires specification of performance criteria and development of appropriate means to measure performance against these criteria. Testing does not always call for the display or recitation of knowledge, but may include skills performance. The criteria used and their means of measurement are usually dictated by the content outline. Measurement of skills performance poses special challenges, but carefully written learning objectives will specify the acceptable level of performance.

Second, it is important also to evaluate the educational program itself. This usually is carried out in two stages. During program development or implementation, those conducting the program need to carry out a formative evaluation including acceptance by the learners, measured achievement of performance criteria and problems in sequencing. On the basis of this assessment, the program can be altered and improvements made.

Finally, it is important to assess the overall success of the program in altering patient behavior. For a good educational program for health providers, it is important not only to measure gains in knowledge and skills, but also to attempt to change actual practice of physicians and daily activities of the patients. While it is difficult to assess this final—and most important—behavioral measure, there is value in making this evaluation, even if on a limited basis.

To evaluate effectiveness in the achievement of the goals and objectives of the total preventive education

program, methods must be developed to assess the following points:

A. *Acquisition of the content and skills* stipulated in the curriculum related to learning activities (for example, objective and subjective examinations).

B. *Degree (quantity) of use of the developed education and learning materials* in preclinical, clinical and graduate programs (for example, periodic survey).

C. *Changes in personal habits and behavior of the teaching faculty* regarding prevention and risk factor modifications that are effected by the introduction or participation in the institution's prevention education program, or both (for example, pre and post surveys).

D. *Changes in the personal habits and behavior of medical students* as a result of program initiation. An assessment of students' assumption of responsibility for their own risk factors (periodic survey) and recognition of their future role status.

E. *Degree (quantity and quality) of institutional participation in setting an example of proper behavior,* that is, changes in food service, publicity regarding the benefits of exercise, encouraging reduced salt intake and cessation of smoking (periodic survey and interview).

F. *Changes in hospital or clinic medical practice* based on audit of risk factor assessment and intervention in the care of either well "patients" or those with overt manifestations of coronary heart disease.

G. *Systematic collection of information on and student evaluation of the teaching program.*

The evaluation of the education program's success can be undertaken through content examinations, surveys and interviews. Since the success of the program, in many respects, involves desired behavioral changes, the frequent gathering and evaluation of information is imperative. Overall program effectiveness, particularly in the area of initiating changes in institutional attitudes, requires regular and relevant reporting of data. It is most important to evaluate both the content and substance of the educational program and the actual changes.

IV. Strategies for the Most Effective Development of Preventive Cardiology Education

Medical schools and other educational institutions may be reluctant to develop courses or clinical training programs limited to one disease and, more specifically, to the prevention of that one disease. This outline defines potential mechanisms whereby educators may increase their emphasis on teaching the general field of preventive medicine, and coordinate and integrate that teaching effort so that it will be more effective in changing the knowledge, skills and attitudes of students and physicians. It is our belief that the primary prevention of coronary artery disease is one of the best, most appropriate and most relevant models for learning such principles of preventive care.

A. Strategies for gaining nationwide attention and credibility:

1. Encourage medical professional organizations to use primary prevention as a theme for future meetings.
2. Invite philanthropic organizations with a known interest in health care and medical education to place high priority upon innovative demonstration projects on prevention.
3. Increase the coverage of preventive medicine in examinations by the National Board of Medical Examiners and specialty Boards.
4. Encourage medical specialty societies to support health education programs in a visible and substantive way.
5. Provide editorials in appropriate journals about the need for improved educational preparation for physicians in primary prevention as well as the need for further research.
6. Encourage those who sponsor continuing medical education programs to increase the coverage of primary prevention in their curricula.
7. Encourage expanding participation in the Preventive Cardiology Academic Awards Program with extensive publicity about the awards given and the results achieved.

B. Strategies for encouraging medical schools to develop programs in preventive cardiology:

1. Institutional officers should receive information on how preventive programs might be appropriately included in cost reimbursement formulae for Medicare/Medicaid and other categorical insurance programs.
2. Medical schools should encourage their faculty to consider applying for academic awards in preventive cardiology.
3. Medical schools should provide brief "case studies" of successful teaching programs in primary prevention. The packages should be distributed broadly to medical school deans, curriculum committees and heads of divisions of cardiology, preventive medicine, epidemiology and self-study accreditation review groups.
4. Granting agencies should develop small grants for the support of innovative approaches to teaching the prevention of coronary heart disease and provide enough of these so that most acceptable applications will be funded. The availability of these grants should be widely announced.
5. Specialty organizations should include in their annual scientific sessions programs related to the need for better training of physicians in the prevention of coronary heart disease.

C. Strategies and specific examples for implementation of a preventive cardiology curriculum:

1. *A recommended content of a preventive cardiology curriculum* is identified in Appendix 1 of this Task Force report. The strategies by which this material can be incorporated and implemented are presented here. Although the content may be similar, the activities at the medical student, house staff and practicing physician levels differ significantly, and variations in approach will be needed to effect learning. The final

common pathway is a change in physician behavior that allows devotion of thought and time to the practice of preventive techniques, both for the individual high risk patient and the community as a whole.

2. *General principles about implementation include:*

a. The ideal time to educate students about prevention is early, prior to their becoming too heavily oriented toward disease and curative medicine. Time during orientation may be used for assessing individual student's personal risks. These data could be used to teach principles of epidemiology. Since the data are the student's own, they should be more meaningful, thereby enhancing student involvement.

b. Techniques beyond didactic presentations should be used, with active participation of the students, such as participation in community screening programs.

c. The preventive cardiology curriculum should be extended throughout the 4 years rather than being given as a single block. For the student with a particular interest, special preventive cardiology electives should be offered. Students should be involved in the planning of such electives.

d. Prevention should be emphasized in the clinical setting during the students' rotation in obstetrics, pediatrics, internal medicine and family practice services. The student taking care of a patient with an acute myocardial infarction should be responsible for discussing the preventability of the disease as well as planning the patient's rehabilitation program.

e. As in all activities, the faculty should serve as role models.

f. Exercise should be encouraged by having a physical activities center on campus.

g. Demonstration about effective community prevention programs should be presented at each level.

3. *Specific examples:*

a. Medical students
   (1) Introduce prevention concepts early in year 1.
   (2) Determine the student's risk profile.
   (3) Provide correlation conferences using coronary heart disease patients.
   (4) Integrate preventive medicine to the basic science curriculum (for example, given this problem, how could it have been prevented?).
   (5) Provide a separate course in epidemiology and preventive medicine.
   (6) Include risk assessment in the Introduction to Disease course.
   (7) Emphasize prevention during clinical rotations.
      (a) Clinical conferences.
      (b) Study of families of patients.
      (c) Risk assessment and management in both hospital and clinic patients.
   (8) Provide models for prevention in the medical school environment.
      (a) Smoking cessation.
      (b) Nutrition modification by involving hospital food services and school cafeteria.
      (c) Campus exercise program.
   (9) Develop preventive cardiology electives.
   (10) Encourage participation in community preventive programs.

b. House staff.
   (1) Incorporate prevention into hospital in-patient experience.
      (a) Routine risk assessment in every admission workup.
      (b) Clinical conferences.
      (c) Consultation service.
      (d) Patient rounds with nutritionists, health educators, etc.
      (e) Medical audit of current performance.
   (2) Incorporate prevention into outpatient clinic experience.
      (a) Routine risk assessment.
      (b) Use of nutritionists, health educators, etc.
      (c) Home health services.
      (d) Medical audit.
   (3) Provide models within hospital setting (hospital smoking policy, for example).
   (4) Provide teaching programs.
      (a) Formal lectures.
      (b) Analysis of current literature on statistics, epidemiology and preventive medicine.
   (5) Increase coverage of prevention in board examinations.

c. Practicing physicians (continuous medical education)
   (1) Increase coverage of prevention in formal courses, lectures, rounds, clinic-pathologic conferences, etc.
   (2) Perform audits of inpatient and office practice with emphasis on prevention.
   (3) Increase coverage of prevention in certification examinations.
   (4) Encourage use of risk assessments and patient education in practice.
   (5) Encourage involvement of physicians in risk factor management programs.
   (6) Increase coverage of prevention in national meetings, journals.

APPENDIX I

Content Outline for Curriculum on Prevention of Coronary Heart Disease

I. Evidence for Association and Rationale for Intervention

A. *Epidemiologic evidence on risk.*
   Nature of epidemiologic process and nature of

intervention studies.
Evidence from clinical, pathologic and animal-experimental research.

B. *Inferences for prevention.*
Approach for health providers based on current knowledge.
Potential value of prevention (lives saved vs. sudden death, income maintained, cost savings to health system, etc.).

C. *Identification of specific risk factors.*
Those alterable vs. those unalterable:
Blood pressure.
Serum lipids.
Cigarette smoking.
Personality types and psychological factors.
Diabetes mellitus and other metabolic disorders.
Use of estrogens in menopause and birth control.
Body weight (adiposity).
Unalterable, but important factors:
Age.
Sex.
Race.
Unspecified genetic aspects.
Factors lacking strong and consistent evidence:
Socio-economic factors.
Stress (as differentiated from personality).
Exercise.

I. Checklist of Key Risk Factors Amenable to Intervention

A. *Blood pressure.*
1. Appropriate levels for intervention.
2. Confirmation of persistent blood pressure elevation.
3. Special problems:
   a. Variable blood pressure.
   b. Children and adolescents.
   c. Elderly with isolated systolic hypertension.
   d. Interaction of blood pressure with other risk factors.
4. Nonpharmacologic therapy:
   a. Weight reduction.
   b. Dietary salt reduction.
   c. Correction of excess alcohol use.
   d. Combination with drugs or alone.
   e. Impediments to success.
5. Pharmacologic therapy:
   a. Setting goals.
   b. Diuretics.
   c. Adrenergic blocking agents.
   d. Vasodilators.
   e. Combination of agents.
   f. Side effects

B. *Serum lipids.*
Roles of low density lipoproteins, very low density lipoproteins and high density lipoproteins.
Problems of measurement and advice as to which measurements (cholesterol, triglycerides, high density lipoprotein).
Dietary approach.
Pharmacologic approach.
Combinations of drugs and diets.
Expectations of therapy.
Special considerations:
Value after symptomatic disease (angina, myocardial infarction, etc.).
Diabetes mellitus.
Fad diets (macrobiotic, "drinking man's," etc.).

C. *Cigarette smoking.*
Which constituents are harmful and what are potential mechanisms?
Threshold level or critical age?
Interaction with other variables
(blood pressure, cholesterol, oral contraceptives, alcohol, body weight).
Problems of stopping.
Therapeutic approaches:
Group therapy.
Role of physician, other support personnel.
Recidivism, strategies to combat measurement of abstinence.

D. *Weight reduction.*
Role in relation to other risk factors (blood pressure, lipids, glycemia, etc.).
Individual vs. group therapy.
Type of diet.
Special problems (eating out, alcohol, smoking).

E. *Exercise.*
Who should have functional testing, stress electrocardiogram?
Type of exercise prescription.
Orthopedic problems and safety.
Expectations of change.

F. *Other therapies.*
Antiplatelet agents.
Antiarrhythmic agents.
Oral contraception cessation.
Stress control/personality alteration.
Factors affecting endothelium.

III. Specific Approaches to Primary Prevention

A. *Screening.*
Who?
When?
How often?
By whom?
What tests?
Use of work site or community resources.
Follow-up for confirmation.

B. *Decision to initiate therapy.*
   Special considerations:
   Genetic background.
   Risk factor profile.
   Age.
   Sex.
   Race.
   Previous cardiovascular disease.
   Associated diseases.

C. *Family and pediatric aspects.*
   1. General approaches for overall disease prevention, health maintenance, health promotion.
   2. Familial clustering of disease because of shared genes and environment:
      Use of patient with premature arteriosclerosis as indicator for families and children at risk.
      Importance of family intervention with respect to diet, smoking, exercise, blood pressure.
      Availability of normative data for children and adolescents with respect to lipids and blood pressure.
         Sex-related changes at adolescence.
         Concept of "tracking" of blood pressure, and weight and use in screening and follow-up.
         Racial differences in risk factors.
         Concept of arteriosclerosis as a disease beginning in childhood.
   3. Genetic aspects of risk factors and coronary heart disease.
      Monogenetic vs. polygenetic and the interaction with environmental factors.
      Specific patterns of inheritance for hyperlipoproteinemia.
      Genetic aspects of high blood pressure.
         Probably multifactorial disease with polygenetic inheritance and strong environmental influence.
         "Salt-sensitive" concept and data from primitive populations.
         Relationship to obesity and body mass.
         Racial differences as a possible mainfestation of genetic selection, as a possible manifestation of environmental differences
      Genetic aspects of other risk factors.
         Vascular endothelium and mesothelial reaction.
         Platelet aggregability.
         Physical activity.
         Cigarette smoking.
         Obesity.
         Diabetes mellitus.
         Rare genetic diseases associated with premature arteriosclerosis (for example progeria, homocystinuria).
   4. The *process* of using the family for case finding and intervention.
      Specific counseling techniques.
      What age children to screen, frequency of screening.
      Hygienic advice to families regarding diet, activity.
      When to intervene in children using drugs:
         Type IIa children.
         Hypertension.

D. *Changing behavior.*
   Knowledge, skills, attitudes as essentials in education.
   Principles of effective behavior modification.
      Relevant.
      Goal setting.
      Reinforcement.
   Adherence.
      Impediments.
      Monitoring.
      Handling problems.
   Individual instruction.
      How managed.
   Group instruction.
      Favorable situations.
      Size of groups.
      Constructive management.
      Peer support systems.
   Use of media.
      Suggested educational materials.
   Teaching skills to patients.
   Reinforcement techniques.
   Importance of follow-up.
   Frequency of follow-up.
   Common problems of interrelationships.

IV. Secondary Prevention

Although this report has dealt with primary prevention, the concept of secondary prevention (that is, prevention of mortality or morbidity, or both) after development of manifest coronary heart disease (acute myocardial infarction, for example) is important for the following reasons:

A. *Risk factors for second episodes* differing from those for the first, for example, "conventional" risk factors vs. arrhythmias.

B. *Risk status of those with stable angina, unstable angina, or resuscitation following arrhythmic death.*

C. *Intervention on conventional risk factors.*
   Cigarette smoking.
   Obesity.
   High blood pressure.
   Serum cholesterol.
      Diet vs. pharmacologic agents.

Potential effect of cholesterol lowering for secondary prevention.
Behavior pattern.

D. *Intervention for secondary prevention.*
Antiarrhythmic agents.
Antiplatelet agents.
Anticoagulant agents.
Beta blocking agents.

I. The Process of Intervention

A. *Commitment by health providers.*

B. *Setting up a system.*
Public action/public health approach.
Individual/group screening.
The role of physicians.
The role of other health providers.

C. *The sequence of individual assessment.*
Screening.
Confirmation.
Intervention plan/setting goals.
Education.
Knowledge.
Skills.
Attitudes.

D. *Impediments to success.*
Lack of commitment by providers or patients.
No follow-up.
No setting of realistic goals.

elemental potassium (as potassium gluconate, 4.68 g) with saccharin and aromatics. Alcohol 5%.

Indications: Kaon Elixir is indicated for the treatment of potassium depletion in patients with hypokalemia, for the treatment of digitalis intoxication, and for the prevention of potassium depletion when the dietary intake of potassium is inadequate. Prophylactic administration may be indicated in patients receiving digitalis and diuretics for the treatment of congestive heart failure; hepatic cirrhosis with ascites; patients with hypertension on long-term diuretic therapy; patients on corticosteroid therapy; hyperaldosteronism states with normal renal function; the nephrotic syndrome; and certain diarrheal states.

Contraindications: Potassium supplements are contraindicated in patients with hyperkalemia. Hyperkalemia may complicate any of the following conditions: Chronic renal failure, systemic acidosis such as diabetic acidosis, acute dehydration, extensive tissue breakdown as in severe burns, adrenal insufficiency, or the administration of a potassium-sparing diuretic (e.g. spironolactone, triamterene).

Warnings: Do not administer full strength. Kaon Elixir may cause gastrointestinal irritation if administered undiluted. In patients with impaired mechanisms for excreting potassium, the administration of potassium salts can produce hyperkalemia and cardiac arrest. Potentially fatal hyperkalemia can develop rapidly and be asymptomatic. The use of potassium salts in any condition which impairs potassium excretion requires particularly careful monitoring of the serum potassium concentration and appropriate dosage adjustment.

Hypokalemia should not be treated by the concomitant administration of potassium salts and a potassium-sparing diuretic (e.g. spironolactone or triamterene).

Precautions: The diagnosis of potassium depletion is ordinarily made by demonstrating hypokalemia in a patient with a clinical history suggesting some cause for potassium depletion. In interpreting the serum potassium level, acute alkalosis per se can produce hypokalemia in the absence of a deficit in total body potassium, while acute acidosis per se can increase the serum potassium concentration into the normal range even in the presence of a reduced total body potassium. The treatment of potassium depletion, particularly in the presence of cardiac disease, renal disease, or acidosis, requires careful attention to acid-base balance and appropriate monitoring of serum electrolytes, the electrocardiogram, and the clinical status of the patient. In hypokalemic states, hypochloremic alkalosis is a possibility that may require chloride as well as potassium supplementation. In these circumstances, potassium replacement with potassium chloride (e.g. Kaochlor 10% Liquid, W-T) may be more advantageous than with other potassium salts.

Adverse Reactions: Nausea, vomiting, diarrhea, and abdominal discomfort have been reported. The symptoms and signs of potassium intoxication include paresthesias of the extremities, flaccid paralysis, listlessness, mental confusion, weakness and heaviness of the legs, fall in blood pressure, cardiac arrhythmias, and heart block.

Overdosage and Treatment of Hyperkalemia: Hyperkalemia can occur from overdosage or during one of several medical conditions. It should be treated immediately by one or more of the following: 1) Intravenous administration of 300 to 500 ml/hr of 10% dextrose solution containing 10-20 units of crystalline insulin per 1,000 ml. 2) administration of sodium or ammonium cycle exchange resins orally or as retention enemas; 3) hemodialysis or peritoneal dialysis; 4) elimination of potassium containing foods. Caution: Digitalis toxicity can occur if the serum potassium is lowered too rapidly.

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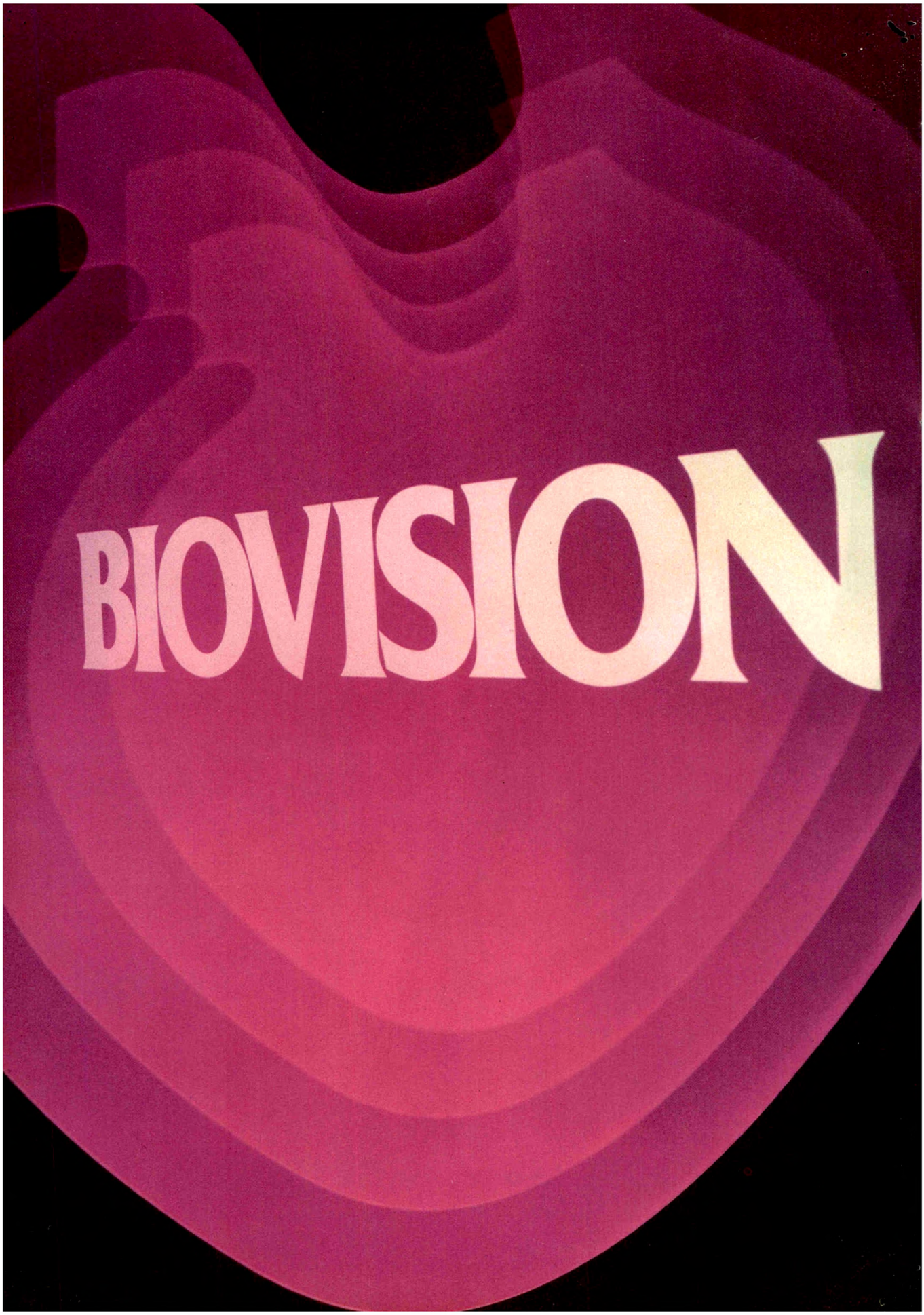
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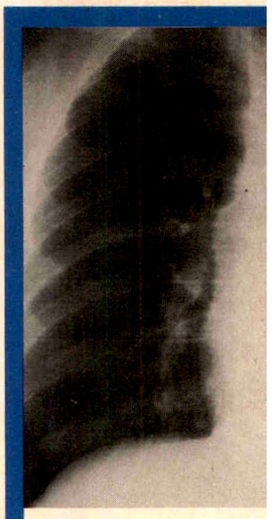

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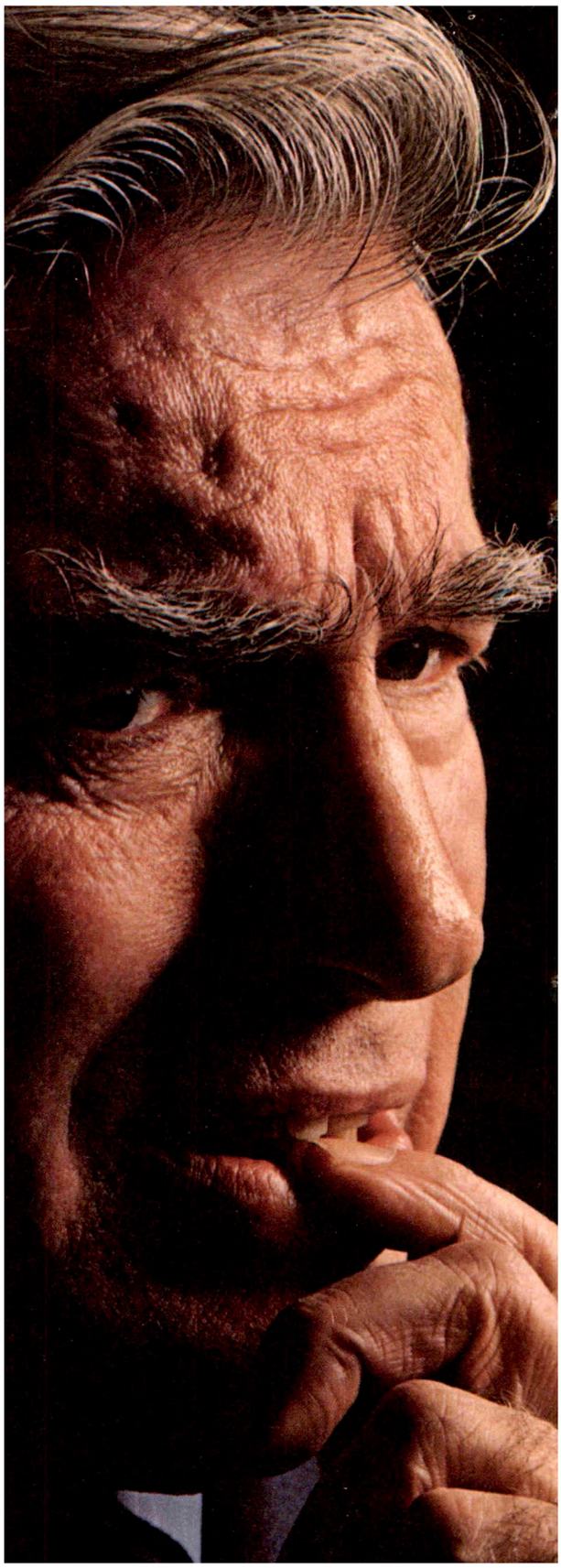

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BEFORE USING INDERAL (PROPRANOLOL HYDROCHLORIDE), THE PHYSICIAN SHOULD BE THOROUGHLY FAMILIAR WITH THE BASIC CONCEPT OF ADRENERGIC RECEPTORS (ALPHA AND BETA), AND THE PHARMACOLOGY OF THIS DRUG.

CONTRAINDICATIONS

INDERAL is contraindicated in: 1) bronchial asthma; 2) allergic rhinitis during the pollen season; 3) sinus bradycardia and greater than first degree block; 4) cardiogenic shock; 5) right ventricular failure secondary to pulmonary hypertension; 6) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL; 7) in patients on adrenergic-augmenting psychotropic drugs (including MAO inhibitors), and during the two week withdrawal period from such drugs.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation is a vital component supporting circulatory function in congestive heart failure, and inhibition with beta-blockade always carries the potential hazard of further depressing myocardial contractility and precipitating cardiac failure. INDERAL acts selectively without abolishing the inotropic action of digitalis on the heart muscle (*i.e.*, that of supporting the strength of myocardial contractions). In patients already receiving digitalis, the positive inotropic action of digitalis may be reduced by INDERAL's negative inotropic effect. The effects of INDERAL and digitalis are additive in depressing AV conduction.

IN PATIENTS WITHOUT A HISTORY OF CARDIAC FAILURE, continued depression of the myocardium over a period of time can, in some cases, lead to cardiac failure. In rare instances, this has been observed during INDERAL therapy. Therefore, at the first sign or symptom of impending cardiac failure, patients should be fully digitalized and/or given a diuretic, and the response observed closely: a) if cardiac failure continues, despite adequate digitalization and diuretic therapy, INDERAL therapy should be immediately withdrawn; b) if tachyarrhythmia is being controlled, patients should be maintained on combined therapy and the patient closely followed until threat of cardiac failure is over.

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuation of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced and the patient carefully monitored. In addition, when INDERAL is prescribed for angina pectoris, the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease, who are given propranolol for other indications.

IN PATIENTS WITH THYROTOXICOSIS, possible deleterious effects from long term use have not been adequately appraised. Special consideration should be given to propranolol's potential for aggravating congestive heart failure. Propranolol may mask the clinical signs of developing or continuing hyperthyroidism or complications and give a false impression of improvement. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. This is another reason for withdrawing propranolol slowly. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

IN PATIENTS DURING ANESTHESIA with agents that require catecholamine release for maintenance of adequate cardiac function, beta blockade will impair the desired inotropic effect. Therefore, INDERAL should be titrated carefully when administered for arrhythmias occurring during anesthesia.

IN PATIENTS UNDERGOING MAJOR SURGERY, beta blockade impairs the ability of the heart to respond to reflex stimuli. For this reason, with the exception of pheochromocytoma, INDERAL should be withdrawn 48 hours prior to surgery, at which time all chemical and physiologic effects are gone according to available evidence. However, in case of emergency surgery, since INDERAL is a competitive inhibitor of beta receptor agonists, its effects can be reversed by administration of such agents, *e.g.*, isoproterenol or levarterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in restarting and maintaining the heart beat has also been reported.

IN PATIENTS PRONE TO NONALLERGIC BRONCHOSPASM (*e.g.*, CHRONIC BRONCHITIS, EMPHYSEMA), INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

DIABETICS AND PATIENTS SUBJECT TO HYPOGLYCEMIA: Because of its beta-adrenergic blocking activity, INDERAL may prevent the appearance of premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia. This is especially important to keep in mind in patients with labile diabetes. Hypoglycemic attacks may be accompanied by a precipitous elevation of blood pressure.

USE IN PREGNANCY: The safe use of INDERAL in human pregnancy has not been established. Use of any drug in pregnancy or women of childbearing potential requires that the possible risk to mother and/or fetus be weighed against the expected therapeutic benefit. Embryotoxic effects have been seen in animal studies at doses about 10 times the maximum recommended human dose.

PRECAUTIONS

Patients receiving catecholamine depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine blocking action of this drug may then produce an excessive reduction of the resting sympathetic nervous activity. Occasionally, the pharmacologic activity of INDERAL may produce hypotension and/or marked bradycardia resulting in vertigo, syncopal attacks, or orthostatic hypotension.

As with any new drug given over prolonged periods, laboratory parameters should be observed at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function.

ADVERSE REACTIONS

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; arterial insufficiency usually of the Raynaud type; thrombocytopenic purpura

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Miscellaneous: reversible alopecia. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been conclusively associated with propranolol.

Clinical Laboratory Test Findings: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DOSAGE AND ADMINISTRATION

The dosage range for INDERAL is different for each indication.

ORAL

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 10-20 mg three or four times daily, before meals and at bedtime, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg per day. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of several weeks. (See WARNINGS.)

PEDIATRIC DOSAGE

At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE OR EXAGGERATED RESPONSE

IN THE EVENT OF OVERDOSAGE OR EXAGGERATED RESPONSE, THE FOLLOWING MEASURES SHOULD BE EMPLOYED:

BRADYCARDIA—ADMINISTER ATROPINE (0.25 to 1.0 mg): IF THERE IS NO RESPONSE TO VAGAL BLOCKADE, ADMINISTER ISOPROTERENOL CAUTIOUSLY.

CARDIAC FAILURE—DIGITALIZATION AND DIURETICS

HYPOTENSION—VASOPRESSORS, *e.g.*, LEVARTERENOL OR EPINEPHRINE (THERE IS EVIDENCE THAT EPINEPHRINE IS THE DRUG OF CHOICE).

BRONCHOSPASM—ADMINISTER ISOPROTERENOL AND AMINOPHYLLINE.

HOW SUPPLIED

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No. 461—Each scored tablet contains 10 mg of propranolol hydrochloride, in bottles of 100 and 1,000. Also in unit dose package of 100.

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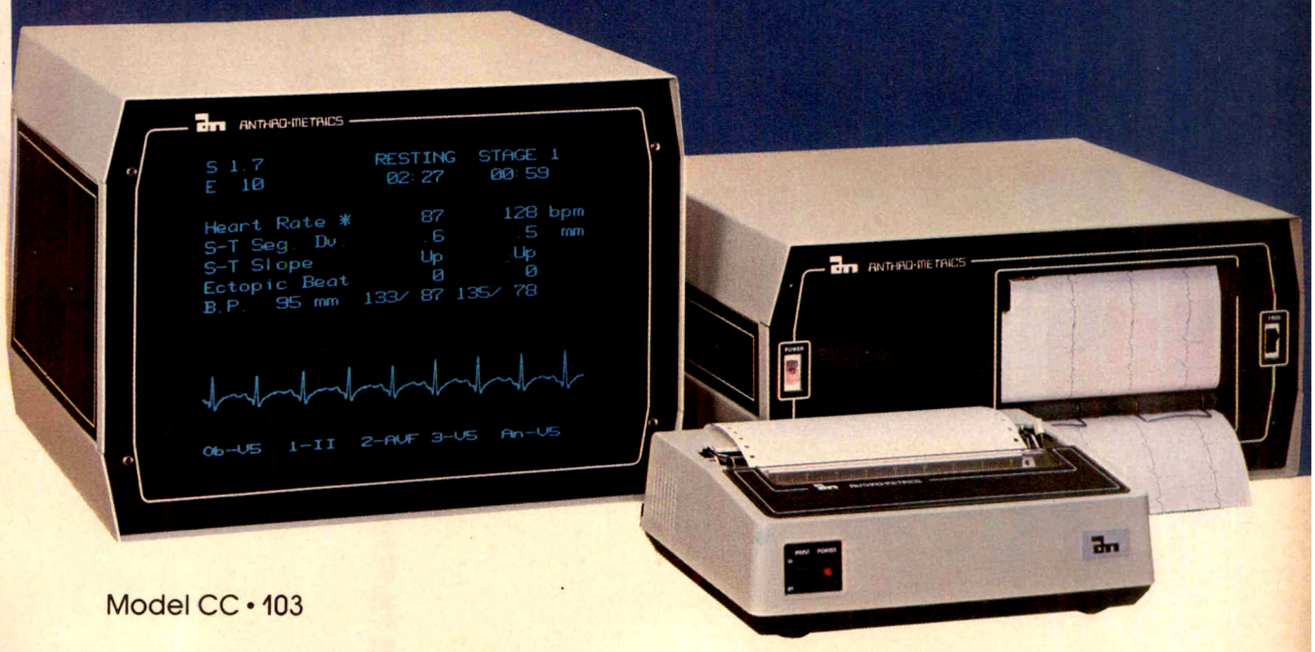

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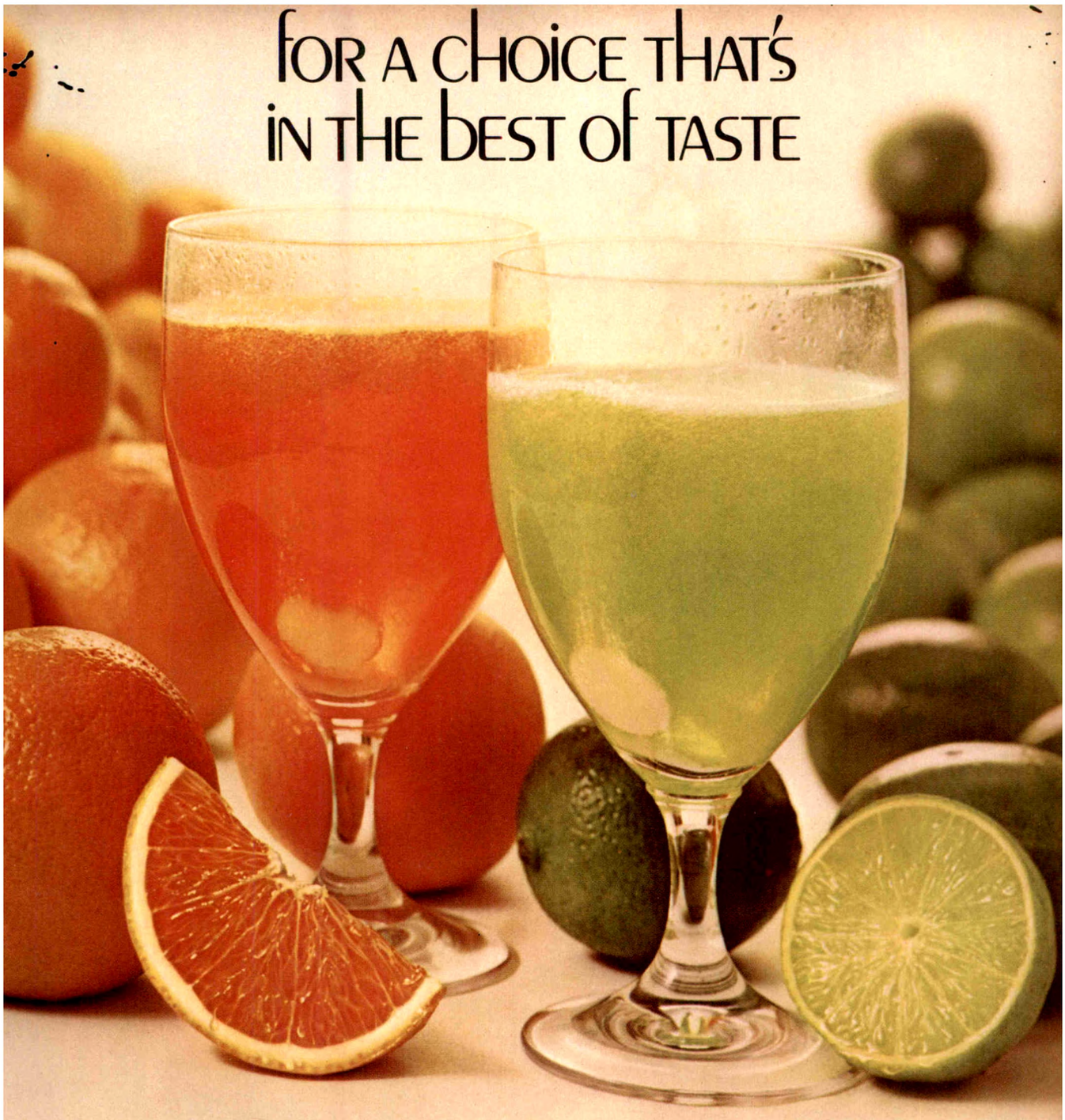

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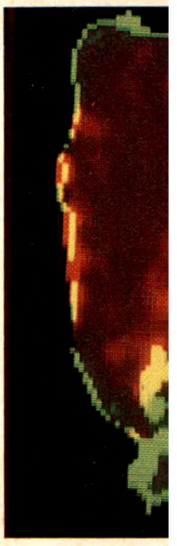

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Brief Summary
Consult the package literature for prescribing information.

Indications and Usage: Dobutrex® (dobutamine hydrochloride, Lilly) is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting either from organic heart disease or from cardiac surgical procedures.

In patients who have atrial fibrillation with rapid ventricular response, a digitalis preparation should be used prior to instituting therapy with Dobutrex.

Contraindication: Dobutrex is contraindicated in patients with idiopathic hypertrophic subaortic stenosis.

Warnings: 1. *Increase in Heart Rate or Blood Pressure*—Dobutrex may cause a marked increase in heart rate or blood pressure, especially systolic pressure. Approximately 10 percent of patients in clinical studies have had rate increases of 30 beats/minute or more, and about 7.5 percent have had a 50-mm Hg or greater increase in systolic pressure. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of developing rapid ventricular response. Patients with preexisting hypertension appear to face an increased risk of developing an exaggerated pressor response.

2. *Ectopic Activity*—Dobutrex may precipitate or exacerbate ventricular ectopic activity, but it rarely has caused ventricular tachycardia.

Precautions: 1. **During the administration of Dobutrex, as with any adrenergic agent, ECG and blood pressure should be continuously monitored. In addition, pulmonary wedge pressure and cardiac output should be monitored whenever possible to aid in the safe and effective infusion of Dobutrex.**

2. Hypovolemia should be corrected with suitable volume expanders before treatment with Dobutrex is instituted.

3. Animal studies indicate that Dobutrex may be ineffective if the patient has recently received a beta-blocking drug. In such a case, the peripheral vascular resistance may increase.

4. No improvement may be observed in the presence of marked mechanical obstruction, such as severe valvular aortic stenosis.

Usage Following Acute Myocardial Infarction—Clinical experience with Dobutrex following myocardial infarction has been insufficient to establish the safety of the drug for this use. There is concern that any agent which increases contractile force and heart rate may increase the size of an infarction by intensifying ischemia, but it is not known whether dobutamine does so.

Usage in Pregnancy—Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility, harm to the fetus, or teratogenic effects due to dobutamine. However, the drug has not been administered to pregnant women and should be used only when the expected benefits clearly outweigh the potential risks to the fetus.

Pediatric Use—The safety and effectiveness of Dobutrex® (dobutamine hydrochloride, Lilly) for use in children have not been studied.

Drug Interactions—There was no evidence of drug interactions in clinical studies in which Dobutrex was administered concurrently with other drugs, including digitalis preparations, furosemide, spironolactone, lidocaine, glyceryl trinitrate, isosorbide dinitrate, morphine, atropine, heparin, protamine, potassium chloride, folic acid, and acetaminophen. Preliminary studies indicate that the concomitant use of dobutamine and nitroprusside results in a higher cardiac output and, usually, a lower pulmonary wedge pressure than when either drug is used alone.

Adverse Reactions: *Increased Heart Rate, Blood Pressure, and Ventricular Ectopic Activity*—A 10 to 20-mm increase in systolic blood pressure and an increase in heart rate of five to 15 beats per minute have been noted in most patients. (See Warnings regarding exaggerated chronotropic and pressor effects.) Approximately 5 percent of patients have had increased premature ventricular beats during infusions. These effects are dose related.

Miscellaneous Uncommon Effects—The following adverse effects have been reported in 1 to 3 percent of patients: nausea, headache, anginal pain, nonspecific chest pain, palpitations, and shortness of breath.

No abnormal laboratory values attributable to Dobutrex have been observed.

Longer-Term Safety—Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Overdosage: In case of overdosage, as evidenced by excessive alteration of blood pressure or by tachycardia, reduce the rate of administration or temporarily discontinue Dobutrex until the patient's condition stabilizes. Because the duration of action of Dobutrex is short, usually no additional remedial measures are necessary.

Administration and Dosage: *Reconstitution and Stability*—Dobutrex® (dobutamine hydrochloride, Lilly) is incompatible with alkaline solutions and should not be mixed with products such as 5% Sodium Bicarbonate Injection.

Dobutrex may be reconstituted with Sterile Water for Injection or 5% Dextrose Injection. To reconstitute, add 10 ml of diluent to Vial No. 7051, Dobutrex, 250 mg. If the material is not completely dissolved, add an additional 10 ml of diluent. The reconstituted solution may be stored under refrigeration for 48 hours or at room temperature for six hours.

Reconstituted Dobutrex must be further diluted to at least 50 ml prior to administration in 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Sodium Lactate Injection. Intravenous solutions should be used within 24 hours.

Solutions containing Dobutrex may exhibit a color that, if present, will increase with time. This color change is due to slight oxidation of the drug, but there is no significant loss of potency during the reconstituted time periods stated above.

Recommended Dosage—The rate of infusion needed to increase cardiac output usually ranges from 2.5 to 10 mcg/kg/min (see table). On rare occasions, infusion rates up to 40 mcg/kg/min have been required to obtain the desired effect.

Rates of Infusion for Concentrations of 250,500, and 1000 mcg/ml

Drug Delivery Rate (mcg/kg/min)	Infusion Delivery Rate 250 mcg/ml* (ml/kg/min)	500 mcg/ml† (ml/kg/min)	1000 mcg/ml‡ (ml/kg/min)
2.5	0.01	0.005	0.0025
5	0.02	0.01	0.005
7.5	0.03	0.015	0.0075
10	0.04	0.02	0.01
12.5	0.05	0.025	0.0125
15	0.06	0.03	0.015

*250 mg per liter of diluent
†500 mg per liter or 250 mg per 500 ml of diluent
‡1000 mg per liter or 250 mg per 250 ml of diluent

The rate of administration and the duration of therapy should be adjusted according to the patient's response, as determined by heart rate, presence of ectopic activity, blood pressure, urine flow, and, whenever possible, measurement of central venous or pulmonary wedge pressure and cardiac output.

Concentrations up to 5000 mcg/ml have been administered to humans (250 mg/50 ml). The final volume administered should be determined by the fluid requirements of the patient.

(081678)

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TREATING MYOCARDIAL INFARCTION AND REDUCING THE THREAT OF THROMBOEMBOLISM

Each year in this country approximately one million people suffer acute myocardial infarctions. Rapid emergency treatment in coronary care units has been credited with reducing by up to one third the mortality among patients hospitalized with acute attacks.[1]

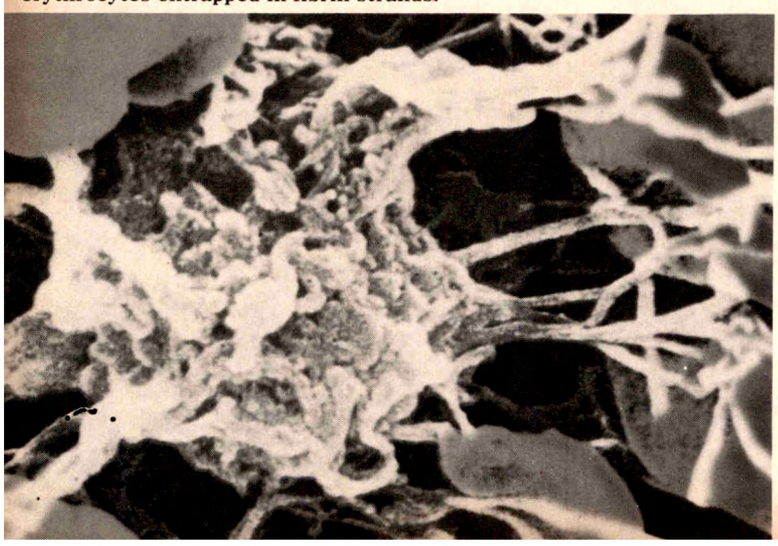
Thrombosis—incidence in myocardial infarction Following the damage to the heart itself, thromboembolism is perhaps the most serious sequel to myocardial infarction.

A study has demonstrated that there is a 39% incidence of calf vein thrombosis during the acute phase of myocardial infarction.[1]

Speed saves lives It has been reported that more than half the thrombi destined to occur in the calf veins form within 72 hours of myocardial infarction, and three-fourths form within the first week. Therefore, a number of investigators have recommended that antithrombotic measures should begin upon admission to the hospital and be effective almost immediately.[2]

Oral anticoagulants have a clinical value It has also been stated that the use of anticoagulants may reduce the frequency of calf vein thrombosis from 22 to 6.5%. The use of anticoagulants is subject to differing opinions regarding improved survival. A number of authorities recommend the use of anticoagulants in *all* patients who have no specific contraindications during the period of hospitalization.[1]

Scanning electron micrograph of 'Red' thrombus, formed by erythrocytes entrapped in fibrin strands.



One team of investigators in M.I. recommends providing full-dose warfarin while the patient is in the hospital and for several days afterward—

if the patient has had prior infarcts or thromboembolism
if the area of infarction is large
if complications (such as CHF or hypotension) require prolonged bed rest.

But, if post myocardial infarction syndrome (Dressler's syndrome) develops, anticoagulants should be discontinued, as pericardial hemorrhage or even cardiac tamponade may develop.[1]

Objectives and benefits of anticoagulation The use of anticoagulants in the acute phase of myocardial infarction has these potential advantages:[2]

prevention of deep vein thrombosis
reduction of embolization from cardiac mural thrombi
prophylaxis against extension of myocardial necrosis or long-term recurrence of infarction
reduction of overall mortality

If anticoagulants can inhibit the formation of deep vein thrombi, then the incidence of pulmonary embolism might be diminished—and pulmonary embolism has been estimated as a threat to life in 5,000 of the 500,000 myocardial infarction patients who are admitted to hospitals in this country each year.[2]

A look at survival One retrospective study of the use of anticoagulants in M.I. evaluated the survival of 1,307 patients from 20 hospitals in a large metropolitan community. The diagnosis of M.I. was based on predefined criteria, which included typical chest pain, serial ECG's, enzyme elevations, and autopsy findings.

Among anticoagulated patients, the adjusted in-hospital case-fatality rate was 18%. For patients who did not receive this treatment, the fatality rate was 31%. For survivors followed for as long as ten years, patients who had been anticoagulated still fared better than those not so treated.[3]

The authors of this study recognize

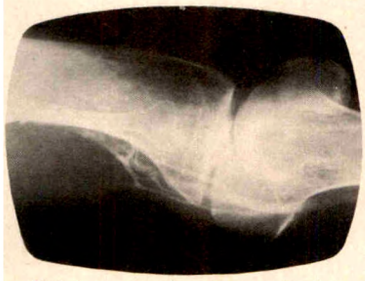
the drawbacks of using retrospective evidence and call for the formation of a multi-center, double-blind, randomized study on the use of anticoagulants in acute myocardial infarction.

Screening the high risk group The risk of DVT (deep vein thrombosis) is particularly great among certain patient groups:

- patients with left ventricular failure
- patients in shock
- patients with arrhythmias
- older patients
- obese patients
- patients with varicose veins
- patients with previous myocardial infarction or thromboembolism

Screening techniques Diagnosis of DVT by physical examination may miss a significant number of clinically silent thrombi. There are, however, additional technological tools to help the clinician define more accurately the incidence of deep vein thrombosis. Among these are:

iodine-125 fibrinogen scanning—radioactively tagged fibrinogen is incorporated into actively forming thrombi and is detected on external sensors. This method is accurate for popliteal and calf vein thrombi, but not for iliofemoral thrombi.[2]



Phlebogram showing occlusion in deep vein of the upper calf.

venography—radiographic evidence of DVT is seen as a constant filling defect in venous projections, abrupt termination of a column of contrast material at a constant site, nonfilling of the deep veins, and presence of flow in collateral veins.[4]

ultrasound—Doppler ultrasound scanning can provide a fast, convenient, inexpensive reading of deep venous obstruction. This technique is potentially the most versatile and accurate method available. However, it demands considerable operator experience to insure maximal accuracy.[5]

impedance plethysmography—this technique results from the observation that blood volume changes in the calf produced by inflation or deflation of a thigh cuff produce variations in electrical resistance (impedance). Such changes are reduced in patients with thrombosis of the popliteal or more proximal veins.[4]

Patient compliance through education Providing the anticoagulated patient with information about his altered physical state and motivating him to comply with the therapeutic regimen constitute one of the most important aspects of health care.[6]

To determine the best way of imparting necessary information about anticoagulation to patients, a test was devised. One group of patients was given a brochure detailing the need for the medication and the importance of following the doctor's instructions. A second group of patients was given a programmed instruction booklet which was quite comprehensive in its teaching content, which included the action of warfarin, the purpose of prothrombin times, how to figure dosage from tablet strengths, possible complications and steps to take to control them.

When tested for learning and retention, the patients in the programmed instruction group scored significantly higher than the group given brochures only. In an area of medicine that relies so heavily on patient compliance, this report could be important in determining how medical information is communicated to the patient.[6]

The bottom line A postmortem study[7] underlines the importance of thrombosis in myocardial infarction. In this study of 173 patients with recurrent myocardial infarction, coronary occlusion due to thrombosis occurred in 54% of cases. Recent occlusive coronary thrombosis was 4 times less frequent in patients who received adequate anticoagulation (mean prothrombin level was 29 ± 5%).

And as one authority states:

"Rational use of anticoagulant therapy in the setting of acute myocardial infarction may save more than 8,000 lives a year in this country. Full advantage should be taken of this therapeutic opportunity."[2]

For prescribing information on COUMADIN® (crystalline warfarin sodium) tablets, including information relating to side effects and contraindications, please see full prescribing information on the following page.

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1. Gazes PC, Gaddy JE: Bedside management of acute myocardial infarction. *Am Heart J 97*(6):782-96, Jun 1979. **2.** Frishman WI, Ribner HS: Anticoagulation in myocardial infarction: Modern approach to an old problem. *Am J Cardiol 43*(6):1207-13, Jun 1979. **3.** Szklo M, *et al:* Additional data favoring use of anticoagulant therapy in myocardial infarction. *JAMA 242*(12):1261-64, Sept 21, 1979. **4.** Hirsch J: Venous thrombosis, in *Anticoagulation: Principles and Practice,* Temple University School of Medicine and Endo Laboratories. **5.** Thrombosis, a symposium. *Contemp Surg 14*:80, 1979. **6.** Rankin MA: Programmed instruction as a patient teaching tool: A study of myocardial infarction patients receiving warfarin. *Heart Lung 8*(3):511-16, May-Jun 1979. **7.** Barrillon A, Kusmierek J, Gerbaux A: Occlusive coronary thrombosis and oral anticoagulants. *Thromb Haemost 41*(1):255-64, Feb 28, 1979.

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COUMADIN is an Endo registered U.S. trademark.

COUMADIN®

crystalline warfarin sodium, U.S.P.*

TABLETS

DESCRIPTION COUMADIN (crystalline warfarin sodium), a prothrombinopenic anticoagulant, is chemically crystalline sodium warfarin isopropanol clathrate. The crystallization of warfarin sodium virtually eliminates trace impurities present in amorphous warfarin sodium, thus achieving a crystalline product of the highest purity. Warfarin* is the coined generic name for 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. On a dose-for-dose basis, COUMADIN (crystalline warfarin sodium) is therapeutically equivalent to amorphous warfarin sodium.

ACTIONS COUMADIN and other coumarin anticoagulants act by depressing synthesis in the liver of several factors which are known to be active in the coagulation mechanisms in a variety of diseases characterized by thromboembolic phenomena. The resultant **in vivo** effect is a sequential depression of Factors VII, IX, X and II. The degree of depression is dependent upon the dosage administered. Anticoagulants have no direct effect on an established thrombus, nor do they reverse ischemic tissue damage. However, once a thrombosis has occurred, anticoagulant treatment aims to prevent further extension of the formed clot and prevents secondary thromboembolic complications which may result in serious and possible fatal sequelae.

After oral administration, absorption is essentially complete, and maximal plasma concentrations are reached in 1 to 9 hours. Approximately 97% is bound to albumin within the plasma. COUMADIN (crystalline warfarin sodium) usually induces hypoprothrombinemia in 36 to 72 hours, and its duration of action may persist for 4 to 5 days, thus producing a smooth, long lasting response curve. Little is known of the metabolic pathways involved in the biotransformation of oral anticoagulants in man. However, their metabolites appear to be eliminated principally in the urine.

INDICATIONS Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: COUMADIN is indicated for the prophylaxis and treatment of venous thrombosis and its extension, the treatment of atrial fibrillation with embolization, the prophylaxis and treatment of pulmonary embolism, and as an adjunct in the treatment of coronary occlusion.

"Possibly" effective: as an adjunct in the treatment of transient cerebral ischemic attacks.

Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS Anticoagulation is contraindicated in any localized or general physical condition or personal circumstance in which the hazard of hemorrhage might be greater than its potential clinical benefits, such as:

Pregnancy—COUMADIN (crystalline warfarin sodium) is contraindicated in pregnancy because the drug passes through the placental barrier and may cause fatal hemorrhage to the fetus in utero. Furthermore, there have been reports of birth malformations in children born to mothers who have been treated with warfarin during pregnancy. Women of childbearing potential who are candidates for anticoagulant therapy should be carefully evaluated and the indications critically reviewed with the patient. If the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the possibility of termination of the pregnancy should be discussed in light of those risks.

Hemorrhagic tendencies or blood dyscrasias. Recent or contemplated surgery of: (1)central nervous system; (2)eye; (3)traumatic surgery resulting in large open surfaces. **Bleeding tendencies associated with active ulceration or overt bleeding of:** (1)gastrointestinal, genitourinary or respiratory tracts; (2)cerebrovascular hemorrhage; (3)aneurysms—cerebral, dissecting aorta; (4)pericarditis and pericardial effusions; (5)subacute bacterial endocarditis. **Threatened abortion,** eclampsia and preeclampsia. **Inadequate laboratory facilities** or unsupervised senility, alcoholism, psychosis; or lack of patient cooperation. **Spinal puncture** and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding. **Miscellaneous:** major regional, lumbar block anesthesia and malignant hypertension.

WARNINGS Warfarin sodium is a potent drug with a half-life of 2½ days; therefore its effects may become more pronounced as daily maintenance doses overlap. It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter. Dosage should be controlled by periodic determinations of prothrombin time or other suitable coagulation tests. Determinations of whole blood clotting and bleeding times are not effective measures for control of therapy. Heparin prolongs the one-stage prothrombin time. Therefore, to obtain a valid prothrombin time when heparin and COUMADIN (crystalline warfarin sodium) are given together, a period of at least 5 hours should elapse after the last intravenous dose and 24 hours after the last subcutaneous dose of heparin, before blood is drawn.

Caution should be observed when warfarin sodium is administered in any situation or physical condition where added risk of hemorrhage is present.

Administration of anticoagulants in the following conditions will be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the risk of thrombosis or embolization in untreated cases. The following may be associated with these increased risks:

Lactation—coumarins may pass into the milk of mothers and cause a prothrombinopenic state in the nursing infant. **Severe to moderate hepatic or renal insufficiency. Infectious diseases or disturbances of intestinal flora**—sprue, antibiotic therapy. **Trauma** which may result in internal bleeding. **Surgery or trauma** resulting in large exposed raw surfaces. **Indwelling catheters. Severe to moderate hypertension. Miscellaneous:** polycythemia vera, vasculitis, severe diabetes, severe allergic and anaphylactic disorders.

Patients with congestive heart failure may become more sensitive to COUMADIN, thereby requiring more frequent laboratory monitoring, and reduced doses of COUMADIN.

Concurrent use of anticoagulants with streptokinase or urokinase is not recommended and may be hazardous. (Please note recommendations accompanying these preparations.)

Abrupt cessation of anticoagulant therapy is not generally recommended; taper dose gradually over three to four weeks.

PRECAUTIONS Periodic determination of prothrombin time or other suitable coagulation test is essential.

Numerous factors, alone or in combination, including travel, changes in diet, environment, physical state and medication may influence response of the patient to anticoagulants. It is generally good practice to monitor the patient's response with additional prothrombin time determinations in the period immediately after discharge from the hospital, and whenever other medications are initiated, discontinued or taken haphazardly. The following factors are listed for your reference; however, other factors may also affect the prothrombin response.

The following factors, alone or in combination, may be responsible for increased prothrombin time response:

ENDOGENOUS FACTORS: Carcinoma; collagen disease; congestive heart failure; diarrhea; elevated temperature; hepatic disorders—infectious hepatitis, jaundice; poor nutritional state; vitamin K deficiency—steatorrhea.

EXOGENOUS FACTORS: Alcohol†; allopurinol; aminosalicylic acid; anabolic steroids; antibiotics; chymotrypsin; chloral hydrate†; chlorpropamide; chymotrypsin; cimetidine; cinchophen; clofibrate; COUMADIN (crystalline warfarin sodium) overdosage; dextran; dextrothyroxine; diazoxide; dietary deficiencies; diuretics†; disulfiram; drugs affecting blood elements, ethacrynic acid; glucagon; hepatotoxic drugs; indomethacin; inhalation anesthetics; mefenamic acid; methyldopa; methylphenidate; metronidazole; monoamine oxidase inhibitors; nalidixic acid; oxolinic acid; oxyphenbutazone; pyrazolones; phenylbutazone; phenyramidol; phenytoin; prolonged hot weather; prolonged narcotics; quinidine; quinine; salicylates; sulfinpyrazone; sulfonamides, long acting; sulindac; thyroid drugs; tolbutamide; triclofos sodium; trimethoprim/sulfamethoxazole; unreliable prothrombin time determinations.

†Present as crystalline sodium warfarin isopropanol clathrate.

†Increased and decreased prothrombin time responses have been reported.

The following factors, alone or in combination, may be responsible for decreased prothrombin time response:

ENDOGENOUS FACTORS: Edema; hereditary resistance to coumarin therapy; hyperlipemia; hypothyroidism.

EXOGENOUS FACTORS: Adrenocortical steroids; alcohol†; antacids; antihistamines; barbiturates; chloral hydrate†; chlordiazepoxide; cholestyramine; COUMADIN (crystalline warfarin sodium) underdosage; diet high in vitamin K; diuretics†; ethchlorvynol; glutethimide; griseofulvin; haloperidol; meprobamate; oral contraceptives; paraldehyde; primidone; rifampin; unreliable prothrombin time determinations; vitamin C.

†Increased and decreased prothrombin time responses have been reported.

A patient may be exposed to a combination of the above factors, some of which may increase and some decrease his sensitivity to COUMADIN. Because the net effect on his prothrombin time response may be unpredictable under these circumstances, more frequent laboratory monitoring is advisable.

Drugs not yet shown to interact or not to interact with coumarins are best regarded with suspicion, and when their administration is started or stopped, the prothrombin time should be determined more often than usual.

Coumarins also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

ADVERSE REACTIONS Potential side effects of COUMADIN (crystalline warfarin sodium) include:

1. Minor or major hemorrhage from any tissue or organ—which is an extension of the physiologic activity of prothrombinopenia. The signs and symptoms will vary according to the location and degree or extent of the bleeding. Therefore the possibility of hemorrhage should be considered in evaluating the condition of any anticoagulated patient with complaints which do not indicate an obvious diagnosis. Bleeding during anticoagulant therapy does not always correlate with prothrombin activity. (See TREATMENT FOR OVERDOSAGE.)

Bleeding which occurs when the prothrombin time is within the therapeutic range warrants diagnostic investigation since it may unmask a previously unsuspected lesion, e.g. tumor, ulcer, etc.

2. Side effects other than hemorrhage are infrequent and consist of alopecia, urticaria, dermatitis, fever, nausea, diarrhea, abdominal cramping, a syndrome called "purple toes," hypersensitivity reactions and a reaction consisting of hemorrhagic infarction and necrosis of the skin.

3. Priapism has been associated with anticoagulant administration, however, a causal relationship has not been established.

DOSAGE AND LABORATORY CONTROL The aim of anticoagulant therapy is to impede the coagulation or clotting mechanism to such an extent that thrombosis will not occur, but at the same time avoiding such extensive impairment as might produce spontaneous bleeding. Effective therapeutic levels with minimal complications can best be achieved in cooperative and well-instructed patients, who keep the doctor informed of their status between visits. COUMADIN (crystalline warfarin sodium) patient aids are available to physicians on request.

The administration and dosage of COUMADIN must be individualized for each patient according to the particular patient's sensitivity to the drug as indicated by the prothrombin time. The prothrombin time reflects the depression of vitamin K dependent Factors VII, X and II. These factors, in addition to Factor IX, are affected by coumarin anticoagulants. There are several modifications of the Quick one-stage prothrombin time and the physician should become familiar with the specific method used in his laboratory.

Administration of COUMADIN should be gauged according to prothrombin time determinations by a suitable method. The blood prothrombin time should usually be determined daily after the administration of the initial dose until prothrombin time results stabilize in the therapeutic range. Intervals between subsequent prothrombin time determinations should be based upon the physician's judgment of the patient's reliability and response to warfarin in order to maintain the individual within the therapeutic range. Acceptable intervals for prothrombin time determinations have usually fallen within the range of one to four weeks. Satisfactory levels for maintenance of therapeutic anticoagulation are 1½ to 2½ times the normal prothrombin time (e.g. 18 to 30 seconds, with a control of 12 seconds).

Induction—40 to 60 mg for average adult or 20 to 30 mg for elderly and/or debilitated patients for one dose only administered orally, intravenously or intramuscularly.

Alternatively, the large priming dose may be decreased for all patients to minimize the possibility of excessive increases in prothrombin time. Induction may be initiated with 10 to 15 mg daily and thereafter (usually 2 or 3 days) adjusted according to prothrombin time response. The basis for the no-loading dose regimen is that the depression of Factors II, IX, and X is not accelerated by the administration of a loading dose.

Maintenance—Most patients are satisfactorily maintained at a dose of 2 to 10 mg daily. Flexibility of dosage is provided by breaking scored tablets in half. The individual dose and interval should be gauged by the patient's prothrombin response.

Duration of therapy—The duration of therapy in each patient should be individualized. In general, anticoagulant therapy should be continued until the danger of thrombosis and embolism has passed.

Treatment during dentistry and surgery—The management of patients who undergo dental and surgical procedures requires close liaison between attending physicians, surgeons and dentists. Interruption of anticoagulant therapy may precipitate thromboembolism, and conversely, if anticoagulants are maintained at full doses, some patients may hemorrhage excessively. If it is elected to administer anticoagulants prior to, during, or immediately following dental or surgical procedures, it is recommended that the dosage of COUMADIN (crystalline warfarin sodium) be adjusted to maintain the prothrombin time at approximately 1½ to 2½ times the control level. The operative site should be sufficiently limited to permit the effective use of local procedures for hemostasis including absorbable hemostatic agents, sutures, and pressure dressings if necessary. Under these conditions dental and surgical procedures may be performed without undue risk of hemorrhage.

COUMADIN with Heparin—Since a delay intervenes between the administration of the initial dose and the therapeutic prolongation of prothrombin time, it may be advisable in emergency situations to administer sodium heparin initially along with COUMADIN. The initial dose of heparin and injectable COUMADIN may be administered together in the same syringe.

It should be noted that heparin may affect the prothrombin time, and therefore, when patients are receiving both heparin and COUMADIN, the blood sample for prothrombin time determination should be drawn just prior to the next heparin dosage, at least 5 hours after the last intravenous injection or 24 hours after the last subcutaneous injection.

TREATMENT FOR OVERDOSAGE Excessive prothrombinopenia, with or without bleeding, is readily controlled by discontinuing COUMADIN (crystalline warfarin sodium), and if necessary, the oral or parenteral administration of vitamin K_1. The appearance of microscopic hematuria, excessive menstrual bleeding, melena, petechiae or oozing from nicks made while shaving are early manifestations of hypoprothrombinemia beyond a safe and satisfactory level.

In excessive prothrombinopenia with mild or no bleeding, omission of one or more doses of COUMADIN may suffice; and if necessary, small doses of vitamin K_1 orally, 2.5 to 10 mg, will usually correct the problem.

If minor bleeding persists, or progresses to frank bleeding, vitamin K_1 in doses of 5 to 25 mg may be given parenterally. (Please note recommendations accompanying vitamin K preparations prior to use.)

Fresh whole blood transfusions should be considered in cases of severe bleeding or prothrombinopenic states unresponsive to vitamin K_1.

Resumption of COUMADIN administration reverses the effect of vitamin K_1, and a therapeutic hypoprothrombinemia level can again be obtained.

SUPPLIED Tablets: COUMADIN (crystalline warfarin sodium, USP). For oral use, single scored, imprinted numerically with potency as follows: 2 mg lavender, 2½ mg orange, 5 mg peach, 7½ mg yellow, 10 mg white. In bottles of 100 and 1000. Also available in Hospital Unit-Dose blister package of 100.

Injection: Available as single injection units of amorphous warfarin sodium lyophilized for intravenous or intramuscular use in a box of 6 units for use immediately after reconstitution.

50 mg: Unit consists of 1 vial, 50 mg; sodium chloride, 10 mg; thimerosal, 0.2 mg. pH is adjusted with sodium hydroxide; accompanied by a 2 ml ampul Sterile Water for Injection.

Sterile Water for Injection contains no antimicrobial or other substance, and it is not suitable for intravascular injection without first having been made approximately isotonic by the addition of a suitable solute. Use only for reconstitution of the lyophilized product.

Injection manufactured by Lypho-Med, Inc., Chicago, Illinois 60651 for Endo Laboratories, Inc.

6037-16 Revised Jan. 1980

COUMADIN is an Endo registered U.S. trademark.

CO-924C Printed in U.S.A. Nov. 1980

Endo Laboratories, Inc.
Subsidiary of the DuPont Company
Garden City, New York 11530

DUPONT

Adult Cardiovascular Training Programs In the United States

This listing is provided as a service to physicians by the American College of Cardiology

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981 Filled	Cardiology Positions 1980–1981 Available	Bed Size
ALABAMA				
Birmingham 35294	University of Alabama Medical Center	14	14	814
Birmingham 35294	Veterans Administration Hospital†	(3)	(3)	499
ARIZONA				
Phoenix 85062	Good Samaritan Hospital Institute for Cardiovascular Disease	5	5	686
Phoenix 85008	Maricopa County General Hospital	3	3	500
Phoenix 85006	St. Luke's Hospital and Medical Center	. . .	. . .	420
Tucson 85724	University of Arizona Health Sciences Center	3	3	. . .
Tucson 85724	University Hospital	. . .	. . .	300
Tucson 85723	Veterans Administration Hospital	. . .	. . .	450
ARKANSAS				
Little Rock 72205	University of Arkansas for Medical Sciences	4	5	391
Little Rock 72206	Veterans Administration Medical Center	. . .	. . .	460
CALIFORNIA				
Davis 95616	University of California Davis Medical Center, Sacramento (UCDMC)	8	8	500
Fresno 93702	Valley Medical Center	2	2	400
Loma Linda 92350	Loma Linda University Medical Center	6	6	525
Loma Linda 92354	Jerry L. Pettis Memorial Veterans Administration Hospital	1	1	400
Long Beach 90801	Memorial Hospital Medical Center	3	4	900
Long Beach 90813	St. Mary Medical Center	4	4	540
Long Beach 90822	Long Beach Veterans Administration Medical Center	7	7	1250
Los Angeles 90048	Cedars-Sinai Medical Center	13	13	1000
Los Angeles 90017	Hospital of the Good Samaritan	3	3	411
Los Angeles 90027	Kaiser Foundation Hospital	6	6	584
Los Angeles 90033	Los Angeles County-University of Southern California Medical Center	5	5	2105
Los Angeles 90059	King-Drew Medical Center	5	5	395
Los Angeles 90057	St. Vincents Medical Center	2	2	. . .
Los Angeles 90057	St. Vincents Medical Center‡	3	3	386
Los Angeles 90024	UCLA Center for the Health Sciences	7	7	770
Los Angeles 90073	Wadsworth Veterans Administration Medical Center	6	6	850
Los Angeles 90033	White Memorial Medical Center	3	3	367
Martinez 94553	Veterans Administration Medical Center	3	3	402
Orange 92668	University of California, Irvine Medical Center	6	6	491
Pasadena 91105	Huntington Memorial Hospital	2	2	565
San Diego 92103	Mercy Hospital and Medical Center	2	2	512
San Diego 92134	Naval Regional Medical Center	9	8	600

* Unless otherwise indicated, all hospitals and insitutions listed have accredited residencies in internal medicine.
† The numbers in parentheses indicate that 3 of the 4 positions listed above are financed by the Veterans Administration Hospital.
‡ No accredited residency in internal medicine.
Address for reprints: American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981 Filled	Cardiology Positions 1980–1981 Available	Bed Size
CALIFORNIA				
San Diego 92103	University of California Medical Center (University Hospital)	6	6	350
La Jolla 92093	Veterans Medical Center	. . .	. . .	450
San Francisco 94129	Letterman Army Medical Center	4	4	425
San Francisco 94120	Mount Zion Hospital & Medical Center	0	2	449
San Francisco 94120	Presbyterian Hospital of Pacific Medical Center	6	6	340
San Francisco 94110	San Francisco General Hospital	2	2	509
San Francisco 94117	St. Mary's Hospital & Medical Center	2	2	555
San Francisco 94143	University of California, San Francisco-Moffitt Hospital	8	8	550
San Francisco 94118	U.S. Public Health Service Hospital	0	2	300
San Francisco 94121	Veterans Administration Medical Center	5	5	360
San Jose 95128	Santa Clara Valley Medical Center	0	1	641
Sepulveda 91343	UCLA-San Fernando Valley Medical Program	4	4	. . .
Sepulveda 91343	Sepulveda Veterans Administration Medical Center	. . .	. . .	881
Van Nuys 91405	Olive View Medical Center	. . .	. . .	123
Stanford 94305	Stanford University Hospital	25	25	594
Palo Alto 94304	Palo Alto Veterans Administration Hospital	. . .	. . .	2000
Torrance 90509	Los Angeles County Harbor-UCLA Medical Center	5	5	510
COLORADO				
Aurora 80045	Fitzsimons Army Medical Center	5	5	450
Denver 80203	St. Luke's Hospital	1	1	460
Denver 80262	University of Colorado Health Science Center	11	11	. . .
Denver 80262	University Hospital	. . .	. . .	350
Denver 80204	Denver General Hospital	. . .	. . .	349
Denver 80262	Denver Veterans Administration Hospital	. . .	. . .	528
Denver 80220	Rose Medical Center	. . .	. . .	330
CONNECTICUT				
Bridgeport 06602	Bridgeport Hospital	2	2	650
Bridgeport 06606	St. Vincent's Medical Center	2	2	390
Farmington 06032	University of Connecticut	6	6	. . .
Farmington 06032	John Dempsey Hospital	(1)	(1)	220
Hartford 06105	Saint Francis Hospital	(3)	(3)	650
New Britain 06050	New Britain General	(1)	(1)	436
Newington 06111	Newington Veterans Administration Hospital	(1)	(1)	190
Hartford 06115	Hartford Hospital	3	4	945
Hartford 06112	Mount Sinai Hospital	2	2	375
New Haven 06511	Hospital of St. Raphael	2	2	500
New Haven 06510	Yale University School of Medicine	10	10	882
West Haven 06516	West Haven VA Medical Center	. . .	. . .	692
Norwalk 06856	Norwalk Hospital	2	2	427
DISTRICT OF COLUMBIA				
Washington, D.C. 20003	D.C. General Hospital	. . .	. . .	557
Washington, D.C. 20003	Georgetown Cardiology Service	2	2	. . .
Washington, D.C. 20003	Howard University Cardiology Division	3	3	. . .
Washington, D.C. 20007	Georgetown University Hospital	8	8	477
Washington, D.C. 20037	George Washington University Hospital	10	10	520
Washington, D.C. 20060	Howard University Hospital	4	4	500
Washington, D.C. 20017	Providence Hospital	2	2	310
Washington, D.C. 20422	Veterans Administration Medical Center	8	8	700
Washington, D.C. 20012	Walter Reed Army Medical Center	8	8	850
Washington, D.C. 20010	Washington Hospital Center	2	2	900
FLORIDA				
Gainesville 32610	University of Florida College of Medicine	7	7	. . .
Gainesville 32610	Shands Teaching Hospital	. . .	. . .	465
Gainesville 32610	Veterans Administration Medical Center	. . .	. . .	480
Jacksonville 32209	University Hospital of Jacksonville	2	2	372
Miami 33101	University of Miami School of Medicine	12	12	. . .
Miami 33136	Jackson Memorial Hospital	. . .	. . .	1250
Miami 33152	University of Miami Hospital and Clinics	. . .	. . .	80
Miami 33125	Miami Veterans Administration Hospital	. . .	. . .	1000
Miami Beach 33140	Mount Sinai Medical Center	10	10	690
Tampa 33612	University of South Florida College of Medicine	6	6	. . .
Tampa 33606	Tampa General Hospital	. . .	. . .	586

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981 Filled	Cardiology Positions 1980–1981 Available	Bed Size
FLORIDA				
Tampa 33612	Veterans Administration Hospital	...	...	697
GEORGIA				
Atlanta 30303	Emory University School of Medicine	31	31	...
Atlanta 30303	Crawford W. Long Hospital	...	...	520
Atlanta 30322	Emory University Hospital	...	...	600
Atlanta 30303	Grady Memorial Hospital	...	...	1004
Decatur 30033	Veterans Administration Hospital	...	...	518
Atlanta 30312	Georgia Baptist Medical Center	1	1	550
Augusta 30912	Medical College of Georgia	8	8	...
Augusta 30912	Eugene Talmadge Memorial Hospital	...	...	380
Augusta 30912	Veterans Administration Hospital	...	...	420
HAWAII				
Honolulu 96813	Queen's Medical Center†	2	2	500
ILLINOIS				
Chicago 60616	Cardiovascular Institute, Michael Reese Hospital and Medical Center	8	8	1000
Chicago 60614	Columbus Hospital	2	2	950
Chicago 60612	Cook County Hospital	5	7	1367
Chicago 60616	Mercy Hospital and Medical Center	4	4	530
Chicago 60608	Mount Sinai Hospital Medical Center	4	4	519
Chicago 60611	Northwestern Memorial Hospital	9	9	1600
Chicago 60611	Veterans Administration/Lakeside	...	...	...
Chicago 60612	Rush-Presbyterian St. Luke's Medical Center	9	9	1166
Chicago 60637	University of Chicago Medical Center	10	10	700
Chicago 60680	University of Illinois Hospital/Abraham Lincoln School of Medicine	12	12	500
Chicago 60680	Westside Veterans Hospital	...	...	800
Evanston 60202	St. Francis Hospital	8	8	485
Maywood 60153	Loyola University Stritch School of Medicine	14	14	500
Hines 60141	Veterans Administration Hospital	...	...	1200
North Chicago 60064	University of Health Sciences/Chicago Medical Center	...	...	...
North Chicago 60064	North Chicago Veterans Administration Medical Center	1	1	250
Great Lakes 60088	Great Lakes Naval Regional Medical Center	1	1	1000
Chicago 60622	Saint Mary of Nazareth Hospital Center	2	2	500
Oak Lawn 60453	Christ Hospital	1	2	850
INDIANA				
Indianapolis 46223	Indiana University School of Medicine	18	18	1500
Indianapolis 46202	Methodist Hospital of Indiana	1	2	1150
Indianapolis 46260	St. Vincent's Hospital	3	3	568
IOWA				
Iowa City 52242	University of Iowa Hospitals and Clinics	13	13	1100
Iowa City 52240	Veterans Administration Hospital	...	...	360
KANSAS				
Kansas City 66103	University of Kansas College of Health Sciences & Hospital	2	2	...
Kansas City 66103	Veterans Administration Hospital	...	...	900
KENTUCKY				
Lexington 40536	University of Kentucky Medical Center	2	6	468
Louisville 40202	University of Louisville School of Medicine	12	12	...
Louisville 40202	Jewish Hospital	...	...	441
Louisville 40202	Norton Hospital	...	...	492
Louisville 40202	University Hospital	...	...	354
Louisville 40202	Veterans Administration Hospital	...	...	444
LOUISIANA				
New Orleans 70112	Louisiana State University Medical Center	5	5	...
New Orleans 70112	Charity Hospital	...	...	1400
New Orleans 70121	Ochsner Clinic	4	6	532
New Orleans 70112	Tulane University Medical Center	10	10	...
New Orleans 70112	Charity Hospital	...	...	1000
New Orleans 70112	University Hospital	...	...	350
New Orleans 70115	Touro Infirmary	...	...	570
New Orleans 70112	Veterans Administration Hospital	...	...	546

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.
† Only research portion is accredited.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981		Bed Size
		Filled	Available	
LOUISIANA				
Shreveport 71130	Louisiana State University Medical Center	0	4	650
Shreveport 71103	Veterans Administration Medical Center	. . .	. . .	449
MAINE				
Portland 04102	Maine Medical Center	3	4	565
MARYLAND				
Baltimore 21205	Johns Hopkins Medical Institutions	20	20	1143
Baltimore 21224	Baltimore City Hospital	2	2	250
Baltimore 21201	Maryland General Hospital	1	1	486
Baltimore 21218	Union Memorial Hospital	1	1	450
Baltimore 21211	U.S. Public Health Service Hospital	3	3	200
Baltimore 21201	University of Maryland Hospital	6	6	800
Bethesda 20014	National Naval Medical Center/Uniformed Services University of the Health Sciences	5	5	450
Cheverly 20785	Prince George's General Hospital & Medical Center	2	2	650
MASSACHUSETTS				
Boston 02215	Beth Israel Hospital	8	8	452
Boston 02118	Boston University Medical Center	13	12	800
Boston 02118	Boston City Hospital	. . .	. . .	. . .
Boston 02118	University Hospital	. . .	. . .	. . .
Boston 02130	Boston Veterans Administration Medical Center	3	3	800
Boston 02124	Carney Hospital	0	1	376
Boston 02114	Massachusetts General Hospital	20	20	1100
Boston 02215	New England Deaconess Hospital	5	5	489
Boston 02115	Peter Bent Brigham Hospital	16	16	680
Boston 02135	St. Elizabeth Hospital of Boston	5	5	385
Boston 02111	Tufts/New England Medical Center	7	7	450
Cambridge 02138	Mount Auburn Hospital	3	3	300
Springfield 01107	Baystate Medical Center	2	2	960
West Roxbury 02132	West Roxbury Veterans Administration Medical Center	6	6	279
West Roxbury 02401	Brockton Veterans Administration Medical Center	1	1	900
Worcester 01605	University of Massachusetts Affiliated Hospitals	11	11	. . .
Worcester 01605	Memorial Hospital†	(2)	(2)	400
Worcester 01604	St. Vincent's Hospital†	(2)	(2)	650
Worcester 01605	University of Massachusetts Medical Center†	(6)	(6)	350
Worcester 01610	Worcester City Hospital†	(1)	(1)	350
MICHIGAN				
Ann Arbor 48109	University of Michigan Medical Center	16	16	. . .
Ann Arbor 48104	St. Joseph Mercy Hospital	. . .	. . .	558
Ann Arbor 48109	University Hospital	. . .	. . .	960
Ann Arbor 48105	Veterans Administration Hospital	. . .	. . .	430
Eloise 48132	Wayne County General Hospital	. . .	. . .	441
Detroit 48202	Henry Ford Hospital	9	9	1000
Detroit 48235	Mount Carmel Mercy Hospital & Medical Center	2	2	570
Detroit 48236	St. John Hospital	4	4	528
Detroit 48235	Sinai Hospital	6	6	675
Detroit 48201	Wayne State University Affiliated Hospitals	9	9	. . .
Allen Park 48101	Veterans Administration Hospital	. . .	. . .	639
Detroit 48226	Detroit General Hospital	. . .	. . .	340
Detroit 48201	Harper-Grace Hospital	. . .	. . .	1400
Detroit 48201	Hutzel Hospital	. . .	. . .	419
Lansing 48909	Michigan State University/Ingham Medical Center	4	4	254
Pontiac 48053	St. Joseph Mercy Hospital	4	4	500
Royal Oak 48072	William Beaumont Hospital	7	7	940
Southfield 48037	Providence Hospital	3	3	455
MINNESOTA				
Minneapolis 55407	Abbott-Northwestern Hospital	1	1	800
Minneapolis 55455	University of Minnesota Hospitals	15	15	790
Minneapolis 55455	Hennepin County Medical Center	. . .	. . .	485
St. Paul 55101	St. Paul-Ramsey Hospital	. . .	. . .	610
Minneapolis 55417	Veterans Administration Medical Center	. . .	. . .	775

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† The numbers in parentheses indicate the number of fellows of the parent organization who train here.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981 Filled	Cardiology Positions 1980–1981 Available	Bed Size
MINNESOTA				
Rochester 55901	Mayo Clinic	17	17	. . .
Rochester 55901	St. Mary's & Methodist Hospitals	. . .	. . .	1848
MISSISSIPPI				
Jackson 39216	University Hospital	2	3	500
Jackson 39216	Veterans Administration Hospital	1	1	498
MISSOURI				
Columbia 65212	University of Missouri Medical Center	4	4	499
Columbia 65201	Harry S. Truman Memorial Veterans Administration Hospital	. . .	. . .	406
Kansas City 64111	Mid-America Heart Institute at St. Luke's Hospital	3	3	665
St. Louis 63110	Jewish Hospital of St. Louis/Washington University Medical School	7	7	665
St. Louis 63104	St. Louis University School of Medicine	7	7	317
St. Louis 63141	St. John's Mercy Medical Center	2	2	604
St. Louis 63125	Veterans Administration Hospital	2	2	388
St. Louis 63112	St. Luke's Hospital	1	2	388
St. Louis 63110	Washington University School of Medicine, Barnes Hospital	9	9	1200
NEBRASKA				
Omaha 68131	Creighton University Cardiac Center/St. Joseph Hospital	7	7	415
Omaha 68105	University of Nebraska Medical Center	2	2	320
NEVADA				
Las Vegas 89102	Southern Nevada Memorial Hospital	2	2	325
NEW HAMPSHIRE				
Hanover 03755	Dartmouth-Hitchcock Medical Center	2	2	. . .
Hanover 03755	Mary Hitchcock Memorial Hospital	. . .	. . .	425
White River Junction, Vermont 05001	Veterans Administration Hospital	. . .	. . .	225
NEW JERSEY				
Browns Mills 08015	Deborah Heart & Lung Center†	20	20	132
East Orange 07019	Veterans Administration Medical Center	4	4	943
Hackensack 07601	Hackensack Hospital	2	2	500
Jersey City 07304	Jersey City Medical Center	2	2	643
Long Branch 07740	Monmouth Medical Center	0	1	600
New Brunswick 08903	New Brunswick Affiliated Hospitals-St. Peter's Medical Center‡	1	1	420
Newark 07103	College of Medicine & Dentistry of New Jersey/New Jersey Medical School	4	4	560
Newark 07112	Newark Beth Israel Medical Center	5	5	500
Newark 07102	St. Michael's Medical Center	7	7	480
Paramus 07652	Bergen Pines County Hospital	2	4	1235
Paterson 07503	St. Joseph's Hospital & Medical Center	1	1	650
Piscataway 08854	College of Medicine & Dentistry of New Jersey-Rutgers Medical School	. . .	. . .	. . .
Green Brook 08812	Raritan Valley Hospital	3	3	130
Lyons 07939	Lyons Veterans Administration Hospital	1	1	150
New Brunswick 08901	Middlesex General Hospital	1	1	350
Summit 07901	Overlook Hospital/Columbia University College of Physicians and Surgeons	2	2	560
NEW MEXICO				
Albuquerque 87131	University of New Mexico Affiliated Hospitals	4	4	. . .
Alburquerque 87108	Lovelace Medical Center	. . .	. . .	244
Alburquerque 87131	University of New Mexico Hospital	. . .	. . .	272
Albuquerque 87108	Veterans Administration Medical Center	. . .	. . .	442
NEW YORK				
Albany 12208	Albany Medical Center Hospital	4	4	800
Albany 12208	Veterans Administration Medical Center	3	3	700
Bronx 10456	Bronx-Lebanon Hospital Center§	3	3	568
Bronx 10461	Hospital of Albert Einstein College of Medicine	8	8	400
Bronx 10461	Bronx Municipal Hospital Center	. . .	. . .	900
Bronx 10451	Lincoln Hospital-New York Medical College	0	1	539
Bronx 10466	Misericordia Hospital Medical Center	2	2	400

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.
† Affiliate—Albert Einstein Medical Center, Philadelphia, Pennsylvania 19141.
‡ Program to be merged with CMDNJ-Rutgers Medical School July 1, 1981.
§ Affiliate of Albert Einstein College of Medicine.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981 Filled	Cardiology Positions 1980–1981 Available	Bed Size
NEW YORK				
Bronx 10467	Montefiore Hospital & Medical Center	10	10	800
Bronx 10467	North Central Bronx	...	...	400
Brooklyn 11212	Brookdale Hospital Medical Center	5	5	1000
Brooklyn 11201	Brooklyn Hospital	4	4	450
Brooklyn 11201	Brooklyn Cumberland Medical Center	...	...	350
Brooklyn 11235	Coney Island Hospital	5	5	560
Brooklyn 11238	Jewish Hospital and Medical Center of Brooklyn	2	2	600
Brooklyn 11203	Kingsbrook Jewish Medical Center	2	2	351
Brooklyn 11201	Long Island College Hospital	4	4	567
Brooklyn 11219	Maimonides Medical Center	4	4	670
Brooklyn 11215	Methodist Hospital	2	2	557
Brooklyn 11203	State University of New York Downstate Medical Center	11	11	...
Brooklyn 11203	Kings County Hospital Medical Center	...	...	900
Brooklyn 11203	State University Hospital	...	...	350
Brooklyn 11209	Veterans Administration Medical Center, Brooklyn	...	...	1000
Buffalo 14203	Buffalo General Hospital	0	1	700
Buffalo 14209	Millard Fillmore Hospital	1	2	711
Buffalo 14215	State University of New York at Buffalo/Erie County Medical Center	3	3	610
Buffalo 14215	Veterans Administration Medical Center	4	4	900
East Meadow 11554	Nassau County Medical Center	6	6	650
Elmhurst 11373	City Hospital at Elmhurst	4	4	804
Far Rockaway 11691	St. John's Episcopal Hospital South Shore Division (affiliated with Long Island Jewish-Hillside Medical Center)	2	2	300
Flushing 11355	Booth Memorial Medical Center	1	1	475
Jamaica 11432	Catholic Medical Center of Brooklyn & Queens	1	2	...
Jamaica 11432	Mary Immaculate Hospital	...	...	264
Brooklyn 11213	St. Mary's Hospital	...	...	237
Rego Park 11373	St. John's Hospital	...	...	250
Jamaica 11418	Jamaica Hospital	1	1	260
Jamaica 11432	Queens General Hospital	2	2	660
Johnson City 13790	C. S. Wilson Memorial Hospital	0	1	476
Manhasset 11030	North Shore University Hospital	4	4	600
Mineola 11501	Nassau Hospital	1	2	53
New Hyde Park 11042	Long Island Jewish-Hillside Medical Center/Queens Hospital Center	6	6	1050
New York 10003	Beth Israel Medical Center	5	5	1028
New York 10003	Cabrini Medical Center	1	1	478
New York 10032	Columbia-Presbyterian Medical Center	12	12	1100
New York 10021	Cornell Medical Center	6	6	...
New York 10021	Memorial Hospital for Cancer & Allied Diseases	...	...	565
New York 10021	New York Hospital	...	...	1095
New York 10037	Harlem Hospital Center	4	4	860
New York 10021	Lenox Hill Hospital	5	5	700
New York 10029	Metropolitan Hospital Center-New York Medical College	3	3	631
New York 10029	Mount Sinai Medical Center	15	15	1300
Bronx 10468	Bronx Veterans Administration Hospital	...	...	702
New York 10016	New York University School of Medicine	8	8	...
New York 10016	Bellevue Hospital	...	...	1261
New York 10016	New York University Hospital	...	...	782
New York 10010	New York Veterans Administration Hospital	4	4	1000
New York 10019	St. Lukes Roosevelt Hospital	3	3	550
New York 10025	St. Luke's Hospital Center	6	6	760
New York 10011	St. Vincent's Hospital & Medical Center of New York	4	4	813
Northport 11768	Northport Veterans Administration Medical Center	4	4	850
Rochester 14621	Rochester General Hospital	1	2	450
Rochester 14611	St. Mary's Hospital	1	1	270
Rochester 14642	University of Rochester Medical Center & Strong Memorial Hospital	10	10	800
Roslyn 11576	St. Francis Hospital†	...	...	227

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.
† Fellowship program starting July 1, 1982.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981 Filled	Cardiology Positions 1980–1981 Available	Bed Size
NEW YORK				
Staten Island 10310	St. Vincents Medical Center-Richmond	2	2	440
Staten Island 10304	U.S. Public Health Service Hospital	2	2	400
Syracuse 13203	St. Joseph's Hospital Health Center	2	3	500
Syracuse 13210	State University of New York-Upstate Medical Center	8	8	. . .
Syracuse 13210	University Hospital	. . .	. . .	350
Syracuse 13210	Veterans Administration Hospital	. . .	. . .	431
Valhalla 10595	New York Medical College-Westchester County Medical Center	5	5	500
NORTH CAROLINA				
Chapel Hill 27514	University of North Carolina School of Medicine	10	10	650
Durham 27710	Duke University Medical Center	31	31	. . .
Durham 27710	Duke University Hospital	. . .	. . .	895
Durham 27706	Veterans Administration Hospital	. . .	. . .	500
Winston-Salem 27103	Bowman Gray School of Medicine-NC Baptist Hospital Medical Center	6	6	688
OHIO				
Akron 44304	Akron City Hospital	0	1	650
Cincinnati 45229	Jewish Hospital	1	1	650
Cincinnati 45267	University of Cincinnati Medical Center	7	7	. . .
Cincinnati 45267	Cincinnati General Hospital	. . .	. . .	690
Cincinnati 45267	Veterans Administration Hospital	. . .	. . .	413
Cleveland 44106	Cleveland Clinic Foundation	30	30	1100
Cleveland 44109	Cleveland Metropolitan General Hospital	4	4	773
Cleveland 44113	Lutheran Medical Center	2	2	286
Cleveland 44106	Mount Sinai Hospital	3	3	550
Cleveland 44104	St. Luke's Hospital	0	1	550
Cleveland 44106	University Hospitals of Cleveland	8	8	. . .
Cleveland 44106	University Hospital	. . .	. . .	900
Cleveland 44106	Veterans Administration Hospital	. . .	. . .	700
Columbus 43222	Mt. Carmel Medical Center	2	2	515
Columbus 43210	Ohio State University Hospital	8	8	1000
Columbus 43214	Riverside Methodist Hospital	2	2	850
Dayton 45406	Good Samaritan Hospital	2	2	522
Dayton 45409	Miami Valley Hospital	1	1	750
Dayton 45428	Veterans Administration Medical Center	2	2	550
Kettering 45429	Kettering Medical Center	1	1	472
Toledo 43699	Medical College of Ohio at Toledo	2	2	280
Toledo 43606	Toledo Hospital	. . .	. . .	740
Youngstown 44501	St. Elizabeth Hospital Medical Center	0	2	756
Youngstown 44502	Youngstown Hospital Association	1	2	1000
OKLAHOMA				
Oklahoma City 73190	University of Oklahoma Health Sciences Center	9	9	320
Oklahoma City 73104	Veterans Administration Medical Center	. . .	. . .	434
Oklahoma City 73012	St. Anthony's Hospital	. . .	. . .	684
Oklahoma City 73112	Baptist Hospital	. . .	. . .	563
OREGON				
Portland 97201	University of Oregon Health Sciences Center	5	5	. . .
Portland 97201	University Hospital	. . .	. . .	450
Portland 97207	Veterans Administration Hospital	. . .	. . .	550
PENNSYLVANIA				
Allentown 18105	Allentown and Sacred Heart Hospital Center	1	2	400
Allentown 18105	Allentown Hospital	. . .	. . .	280
Danville 17821	Geisinger Medical Center	3	4	500
Hershey 17033	Pennsylvania State University College of Medicine-Milton S. Hershey Medical Center	7	7	350
Philadelphia 19141	Albert Einstein Medical Center†	6	6	619
Philadelphia 19125	Episcopal Hospital	1	1	294
Philadelphia 19146	Graduate Hospital	1	3	320
Philadelphia 19102	Hahnemann Medical College & Hospital	6	6	550
Philadelphia 19151	Lankenau Hospital	6	6	450
Philadelphia 19129	Medical College of Pennsylvania Hospital	9	9	367
Philadelphia 19104	Presbyterian-University of Pennsylvania Medical Center	7	7	425
Philadelphia 19140	Temple University Health Sciences Center	7	7	500

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.
† Affiliate—Deborah Heart & Lung Center, Browns Mills, New Jersey 08015.

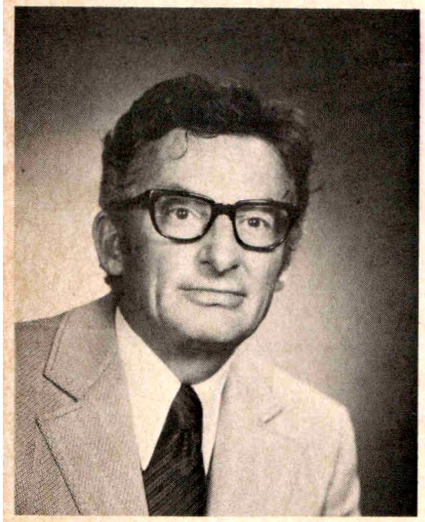
State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981		Bed Size
		Filled	Available	
PENNSYLVANIA				
Philadelphia 19107	Thomas Jefferson University Hospital	7	7	550
Philadelphia 19104	University of Pennsylvania	15	15	. . .
Philadelphia 19104	Hospital of the University of Pennsylvania	. . .	. . .	694
Philadelphia 19104	Veterans Administration Medical Center	. . .	. . .	490
Pittsburgh 15212	Allegheny General Hospital	8	8	726
Pittsburgh 15219	Mercy Hospital	1	2	610
Pittsburgh 15213	Montefiore Hospital	2	2	433
Pittsburgh 15201	St. Francis General Hospital	4	4	750
Pittsburgh 15215	St. Margaret Memorial Hospital	. . .	. . .	150
Pittsburgh 15232	Shadyside Hospital	2	2	450
Pittsburgh 15261	University of Pittsburgh Health Center Hospitals	7	8	. . .
Pittsburgh 15213	Presbyterian-University Hospital	. . .	. . .	554
Pittsburgh 15240	Veterans Administration Medical Center (Oakland Division)	. . .	. . .	390
Pittsburgh 15224	Western Pennsylvania Hospital	2	2	680
Sayre 18840	Guthrie Clinic/Robert Packer Hospital	0	2	323
PUERTO RICO				
Ponce 00731	Ponce District General Hospital	2	4	541
Rio Piedras 00935	San Juan City Hospital/Puerto Rico Medical Center	3	3	500+
San Juan 00936	University of Puerto Rico, School of Medicine/University Hospital	5	6	535
San Juan 00936	Veterans Administration Hospital	3	3	750
RHODE ISLAND				
Pawtucket 02860	Memorial Hospital†	(5)	(5)	306
Providence 02906	The Miriam Hospital†	. . .	. . .	247
Providence 02902	Rhode Island Hospital	5	5	719
SOUTH CAROLINA				
Charleston 29403	Medical University of South Carolina Teaching Hospitals	7	7	. . .
Charleston 29403	Charleston County Hospital	. . .	. . .	154
Charleston 29403	Medical University Hospital	. . .	. . .	534
Charleston 29403	Veterans Administration Hospital	. . .	. . .	407
TENNESSEE				
Memphis 38163	University of Tennessee Center for the Health Sciences	8	8	. . .
Memphis 38163	Baptist Memorial	. . .	. . .	1920
Memphis 38103	City of Memphis Hospital	. . .	. . .	540
Memphis 38163	University of Tennessee Hospital	. . .	. . .	180
Memphis 38104	Veterans Administration Hospital	. . .	. . .	923
Nashville 37208	Meharry Medical College	0	1	400
Nashville 37232	Vanderbilt Medical Center	9	9	. . .
Nashville 37210	Nashville General Hospital	. . .	. . .	220
Nashville 37205	St. Thomas Hospital	. . .	. . .	500
Nashville 37232	Vanderbilt University Hospital	. . .	. . .	510
Nashville 37203	Veterans Administration Hospital	. . .	. . .	450
TEXAS				
Dallas 75246	Baylor University Medical Center	7	7	1300
Dallas 75235	Parkland Hospital and University of Texas Health Science Center at Dallas	28	28	2900
Dallas 75235	Children's Hospital	. . .	. . .	117
Dallas 75235	Presbyterian Hospital	. . .	. . .	700
Dallas 75235	St. Paul's Hospital	. . .	. . .	500
Dallas 75235	Veterans Administration Hospital	. . .	. . .	739
Galveston 77550	University of Texas Medical Branch	3	3	1100
Houston 77030	Baylor College of Medicine	19	19	. . .
Houston 77030	Ben Taub General Hospital	. . .	. . .	475
Houston 77210	Houston Veterans Administration Hospital	. . .	. . .	1296
Houston 77030	Methodist Hospital	. . .	. . .	1050
Houston 77030	St. Luke's Episcopal Hospital/Texas Heart Institute	16	16	. . .
Houston 77030	St. Luke's Episcopal Hospital	. . .	. . .	821
Houston 77030	Texas Children's Hospital	. . .	. . .	328
Houston 77025	University of Texas Medical School at Houston/Hermann Hospital	1	6	800
Lackland Air Force Base 78236	Wilford Hall USAF Medical Center	2	4	1000
San Antonio 78234	Brooke Army Medical Center	8	8	650

* Unless otherwise indicated, all hospitals and institutions listed have accredited residencies in internal medicine.
† These Fellowships are equally shared by both hospitals.

State/City/Zip Code	Hospital/Institution*	Cardiology Positions 1980–1981		Bed Size
		Filled	Available	
TEXAS				
San Antonio 78284	University of Texas Health Science Center at San Antonio	12	12	1150
Temple 76501	Scott and White Memorial Hospital	1	1	425
UTAH				
Salt Lake City 84132	University of Utah Medical Center and Affiliated Hospitals	...	...	...
Salt Lake City 84102	Holy Cross Hospital	1	1	343
Salt Lake City 84104	Latter Day Saints Hospital	1	2	570
Ogden 84403	McKay-Dee Hospital	1	1	360
Salt Lake City 84132	University of Utah Hospital	1	1	300
Salt Lake City 84113	Veterans Administration Hospital	2	2	573
VERMONT				
Burlington 05401	Medical Center Hospital of Vermont, University of Vermont College of Medicine	6	6	500
VIRGINIA				
Charlottesville 22908	University of Virginia Medical Center	8	8	694
Richmond 23298	Medical College of Virginia	9	9	900
Richmond 23249	McGuire Veterans Administration Hospital	...	...	725
WASHINGTON				
Seattle 98195	University of Washington School of Medicine	9	10	...
Seattle 98104	Harborview Medical Center	...	...	305
Seattle 98195	University Hospital	...	...	340
Seattle 98114	Seattle U.S. Public Health Service Hospital	...	...	275
Seattle 98195	Seattle Veterans Administration Hospital	...	...	320
WEST VIRGINIA				
Charleston 25304	Charleston Area Medical Center	0	1	901
Morgantown 26505	West Virginia University Medical Center	3	3	448
WISCONSIN				
Madison 53705	Middleton Memorial Veterans Hospital	3	3	350
Madison 53705	University of Wisconsin Hospital	2	2	536
Milwaukee 53226	Medical College of Wisconsin	8	8	...
Milwaukee 53226	Milwaukee County Medical Complex	...	...	450
Milwaukee 53215	St. Luke's Hospital	...	...	600
Milwaukee 53193	Wood Veterans Administration Hospital	...	...	850
Milwaukee 53233	Mount Sinai Medical Center	5	5	385

* Unless otherwise indicated, all hospitals and institutions have accredited residencies in internal medicine.

President's Page: Professional Societies and Industry



Robert O. Brandenburg, MD, FACC

The medical profession and medical industry have important reasons to complement each other. The goals of both are the same—to enhance the care of the patient who is ill and to prevent illness, when possible. This comment recognizes that if the industry's product is successful it will allow the company to flourish. While there are innumerable examples of advances in medical knowledge that have resulted from the support or cooperation of industry with the profession, this relationship has not reached an optimal level and some problems have developed at the interface of industry and our annual scientific meetings. Before I address this problem, I will make some observations on another area involving technology.

In the area of cardiovascular diseases, the technical developments in the last two decades have been particularly striking. These have resulted in major advances in our ability to recognize altered pathophysiology in patients with cardiovascular disease and better means of control of many cardiovascular problems. An unfortunate effect of these developments, yet to be resolved, is the expense and overlap of many of them. More important has been the decrease in clinical skills of many physicians as the tendency to become a technician instead of a clinician has grown. This unfortunate situation is furthered by federal and private funding agencies that underestimate and underreimburse the time, judgment and experience required to master the outpourings of our new machines. The problem tends to perpetuate itself, because our medical students observe and mimic, as well as note the economic advantage of being a "technician." This "negative" result of medical progress is a separate and important problem for the profession to resolve, and will not be further addressed here.

Rapid technologic development invariably leads to competition. This has been particularly true of the pacemaker industry with remarkably sophisticated units for multiple specific cardiac arrhythmia and conduction defects now available. Competition has led to increases in the number of companies, and a sharp increase in the activities of the marketing division of some of these companies. One consequence of this competition has been related to the replacement of hospitality suites (with a limited expenditure of space and money) at annual scientific meetings with large ballroom entertainment shows of the Las Vegas type with extensive arrays of food, beverages and name entertainers.

The expenditure of many thousands of dollars for these entertainments seems inappropriate at a professional scientific meeting. How much more relevant and beneficial would be the expenditure of such sums for the support of selective educational programs. It is recognized that a "marriage" of this type must give the supporting company appropriate exposure to its physician patrons while the professional society must retain the responsibility for establishing the ground rules for the expenditure and the maintenance of quality control.

It will be our responsibility to come forth with new, creative, innovative educational projects that will be attractive to industry, ones that will replace the lavish, expensive and inappropriate evenings seen at our annual meetings in recent years. Perpetuation of the current format will lead to ill feeling between industry and the profession, perpetuate a "bad image" and certainly will lead to restriction of this type of function at our meetings. The opportunity and need for change is apparent and will be of benefit to all concerned. I am pleased to report that in the past year we have had a meaningful dialog with several of the pacemaker companies. The results of these meetings, in most instances, will be reflected at our future annual scientific sessions.

Looking to the future, I believe that the opportunity and need for collaboration between the medical profession and industry has never been greater. As the funding for medical research becomes increasingly difficult it would appear appropriate, timely and to the advantage of both parties to explore and develop a relationship to enhance this endeavor.

Robert O. Brandenburg, MD, FACC
President
American College of Cardiology

CALENDAR OF EXTRAMURAL PROGRAMS

The aim of each program is to increase the theoretical and practical knowledge of the normal and abnormal function of the cardiovascular system in man. Most of the programs are pertinent to direct care of patients with heart disease. The need for such programs increases with the ever increasing amount of scientific and clinical data, the constant changes in technology and methodology, and the greater availability of therapeutic options. Today most cardiologists, internists and family practitioners feel the need of supplementing their professional reading by direct contact with the authors, research workers and leaders in the field.

To solve these problems the Committee selects each year series of carefully supervised programs which are usually preceded by extensive consultations with the program directors recruited among the foremost specialists educators and scientists in the field of clinical cardiology and allied basic science disciplines.

Although each program director is personally responsible for the choice of faculty, and the structure of the program, the Continuing Education Committee for Extramural Programs assumes the overall responsibility for the caliber of the postgraduate education and the relevance to the practice of cardiology. This is accomplished by the processes of meticulous scrutiny of the objectives, analysis of the educational methods, and studying the impact of each course on the knowledge and attitudes of the participants.

These programs should help each physician to keep up with the new knowledge, to put into practice the new advances and to retract gracefully from the obsolete and useless practices. An effective practitioner must learn and relearn, listen to new ideas, share past experiences and observe the work of his peers. The Continuing Education Committee for Extramural Programs of the American College of Cardiology believes that these goals can be accomplished by all members and nonmember professionals participating in our continuing education programs.

Leonard S. Dreifus, MD, FACC
Chairman, Continuing Education Committee for Extramural Programs

Programs and faculty are subject to change. For further information write Registration Secretary, Extramural Programs Department, American College of Cardiology, Heart House, 9111 Old Georgetown Road, Bethesda, Maryland 20014.

MARCH THROUGH AUGUST 1981

1981

To be arranged individually — **Preceptorships in Cardiology.** Arthur Selzer, FACC, director, Pacific Medical Center, San Francisco, CA

To be arranged individually — **Preceptorships in Cardiology.** Jules Constant, FACC, director. Buffalo General Hospital, Buffalo, NY

MAR. 30–APR. 3 — **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiological Approach.** Charles Fisch, FACC and Douglas P. Zipes, FACC, directors. Krannert Institute of Cardiology, Indiana University Medical Center, Indianapolis, IN

APR. 6–15 — **Cardiology for the Consultant: A Clinician's Retreat.** E. Grey Dimond, FACC and James E. Crockett, FACC, directors. Rancho Santa Fe Inn, Rancho Santa Fe, CA

APR. 16–18 — **New Diagnostic and Therapeutic Modalities in Cardiology.** Edmund H. Sonnenblick, FACC and James Scheuer, FACC, directors. Grand Hyatt New York, New York, NY

APR. 23–24 — **Contemporary Phonocardiography (With Echocardiographic Correlation).** Morton E. Tavel, FACC, director. Methodist Hospital, Indianapolis, IN

APR. 27–MAY 1 — **Consultant's Course in Cardiology.** Richard Gorlin, FACC, Louis E. Teicholz, FACC, Simon Dack, FACC and Ephraim Donoso, FACC, directors. Mount Sinai Medical Center, New York, NY

APR. 29–MAY 1 — **Vectorcardiography—An Advanced Workshop.** Alberto Benchimol, FACC, director. Scottsdale Hilton Hotel, Scottsdale, AZ

MAY 7–9 — **The Pathology of Acquired Diseases of the Heart and Conduction System.** Jesse E. Edwards, FACC, Maurice Lev, FACC and Saroja Bharati, FACC, directors. Radisson Hotel, St. Paul, MN

MAY 7–9 — **Cardiac Emergencies.** Arthur Selzer, FACC and Richard Pasternak, co-directors. The Mark Hopkins, San Francisco, CA

MAY 7–9 — **Practical Cardiology for the Primary Care Physician,** Leonard S. Dreifus, FACC and Joel Morganroth, FACC, directors. Sarasota Hyatt Hotel, Sarasota, FL

MAY 13–15 — **Clinical Auscultation of the Heart.** W. Proctor Harvey, FACC, director and Antonio C. de Leon, Jr., FACC and John F. Stapleton, co-directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington DC

MAY 14–16 — **Cardiac Diagnostic Techniques—A Clinical Perspective.** Arnold M. Weissler, FACC and Nicholas Z. Kerin, FACC, directors and Franklin E. Hull, FACC, S. C. Khullar, FACC and Melvin Rubenfire, FACC, co-directors. Detroit Plaza Hotel, Renaissance Center, Detroit, MI

MAY 18–22 — **Modern Cardiology.** J. Willis Hurst, FACC and Robert C. Schlant, FACC, directors. Sheraton Atlanta Hotel, Atlanta, GA

MAY 28–31 — **Sixth Annual Symposium on Cardiovascular Nursing.** Henry J. L. Marriott, FACC and Leo Schamroth, FACC, directors. Sheraton Sand Key Hotel, Clearwater Beach, FL

JUNE 17–19 — **The Patient with Arrhythmia—A Clinical Approach.** Ross D. Fletcher, FACC and W. Proctor Harvey, FACC, directors. Gorman Building Auditorium, Georgetown University Medical Center, Washington, DC

JUNE 30–JULY 3 — **Eighth Annual Symposium on Clinical Echocardiography: Current Applications and New Developments.** Arthur D. Hagan, FACC, director and Anthony N. DeMaria, FACC and William F. Friedman, FACC, co-directors. Snowbird Conference Center, Snowbird Ski and Summer Resort, Snowbird, UT

AUG. 29–31 — **Tutorials in the Tetons: Clinical Cardiology: Diagnostic and Therapeutic Advances (Seventh Annual).** Robert S. Eliot, FACC, director and James C. Buell, Timothy Fleming, FACC and Gerald L. Wolf, co-directors. Jackson Lake Lodge, Moran, WY

LEARNING CENTER: PROGRAM CALENDAR

The American College of Cardiology's Learning Center is located at the College's headquarters in Bethesda, Maryland. The purpose of the Learning Center is to support professional commitment to quality patient care by providing a standard of excellence in continuing medical education.

For additional information or a complete program calendar, contact the Program Registrar, Heart House Learning Center, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone (301) 897-5400.

LEARNING CENTER PROGRAMS: MARCH THROUGH JULY 1981

Program Number	Date	Program Director	Title of Program
312	March 2–4	Nanette K. Wenger, MD	Rehabilitation of the Coronary Patient
313	March 30–31	Jere H. Mitchell, MD	Cardiovascular Benefits and Risks of Exercise
314	April 1–3	J. O'Neal Humphries, MD	Coronary Heart Disease: New Management Methods
315	April 8–10	Victor Parsonnet, MD	Current Concepts in Pacing
316	April 13–15	Keith Cohn, MD	Exercise Testing: Diagnostic and Physiologic Considerations
317	April 20–22	Pravin M. Shah, MD	Current Applications of Echocardiography: M-Mode, 2-Dimensional and Pulsed Doppler Techniques
318	April 23–25	Daniel S. Berman, MD	Nuclear Cardiology
319	April 27–28	Leonard S. Dreifus, MD and Frits L. Meijler, MD	Computer Electrocardiology: Present Status and Hope for the Future
320	April 30, May 1–2	John A. Spittell, MD	Peripheral Vascular Disease
321	May 6–8	Marvin Dunn, MD	Diagnosis and Management of Common Cardiac Arrhythmias
322	May 11–13	Abdul J. Tajik, MD and James B. Seward, MD	The Role of Two-Dimensional Echocardiography in the Clinical Practice of Cardiology
323	May 14–16	G. Charles Oliver, MD	Ubiquitous PVC
324	May 18–20	William J. Mandel, MD	His Bundle Electrocardiography: Contributions to the Clinical Understanding of the Electrocardiogram
325	May 28–29	Robert O. Brandenburg, MD	Cardiology for the Consultant
326	June 1–3	Shahbudin H. Rahimtoola, MD	Valvular Heart Disease: Current Controversies in Patient Management
327	June 11–13	Robert G. Tancredi, MD	Management of Pulmonary, Renal and Electrolyte Disorders in Cardiac Patients
329	June 15–17	Robert A. O'Rourke, MD	Detection of Cardiac Disease by Physical Examination
302	June 22–24	Paul C. Gillette, MD	Decisions in Clinical Pediatric Cardiac Surgery
331	June 29–30, July 1	B. Leonard Holman, MD	Nuclear Cardiology
330	July 8–10	Michael R. Rosen, MD	Clinical Pharmacology and Electrophysiology of Antiarrhythmic Drugs

CARDIOLOGY BOARD REVIEW: Update in Cardiology

September 9–11, 1981 **Atlanta, Georgia**

Presented by: The American College of Cardiology

Directors: **J. WILLIS HURST, MD, FACC and ROBERT C. SCHLANT, MD, FACC**

For brochure and further information contact: Registration Secretary, Extramural Programs Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20014. Telephone: Area Code 301 897-5400

ANNOUNCEMENT OF 1981 PEDIATRIC CARDIOLOGY EXAMINATION

The Sub-Board of Pediatric Cardiology of the American Board of Pediatrics will offer its next written examination on Friday, July 10, 1981.

The following criteria must be met to qualify to sit for the examination:

1. Certification by the American Board of Pediatrics;
2. Two years of full-time graduate training in an accredited pediatric cardiology program;
3. Letters of recommendation from individuals able to attest to the applicant's fellowship training.

Candidates who achieve a qualifying score on the written examination will be eligible for the oral examination. The oral portion of the examination will be held in October 1981, in New Orleans. A candidate must be successful on both the written and oral portions of the examination in order to be certified.

The registration period for the examination will extend from December 1, 1980 to March 31, 1981. Please contact the American Board of Pediatrics during that time if you wish to receive an application for the examination.

The application fee for the written portion of the examination is $300 ($150 processing, $50 registration, $100 examination fee). An additional fee of $150 will be payable upon receipt of an appointment for the oral examination.

Please direct inquiries to: American Board of Pediatrics
Suite 402, NCNB Plaza
136 East Rosemary Street
Chapel Hill, NC 27514
(919) 929-0461

NSTRUCTIONS FOR AUTHORS

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HE WHOLE PAPER

Address manuscript to Managing Editor, nerican Journal of Cardiology, 666 Fifth e., New York, NY 10103.

Submit two copies of all elements of the ticle: text, references, legends, tables and jures.

Arrange the paper in this order: (1) title ge; (2) abstract; (3) text; (4) references; (5) gends; (6) tables; and (7) figures.

Number all pages in above sequence, beginning with title page as 1, abstract as 2, c.

Type all matter: (1) on 8½ × 11 opaque hite bond paper; (2) in duplicate; (3) on one de of each sheet only; (4) double-space; (5) ave wide margins, all four sides.

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Include first names, degrees and, where plicable, FACC for all authors.

Provide a short running title of 3 to 6 ords.

Insert at bottom: name and address of institution from which work originated plus information about grants.

Add at bottom the phrase "Address for reints: . . ." followed by full name and address th zip code.

HE ABSTRACT

Limit words as follows: 100 to 250 words for ajor articles; 50 to 100 words for case rts.

Add at end of abstract: list of 2 to 6 key ords and subjects for indexing.

HE TEXT

Type in duplicate; double-space.

Do not use abbreviations such as SVC, PW: write out superior vena cava, Wolff-rkinson-White.

Abbreviate measurements (mm, kcal and e like) as recommended in *Uniform Requirements for Manuscripts Submitted to omedical Journals,* published in *Am Rev spir Dis* 1979; 119:3–10; *Ann Intern Med* 79; 90:95–9; *Br Med J* 1979; 1:532–5; and *ncet* 1979:1:428–30.

- Cite in numerical order every reference, figure and table. (Order of mention in text determines the number given to each.)
- Place acknowledgments at end of text, before references.

THE REFERENCES

- Type in duplicate; double-space.
- Number the references in order in which they are mentioned in text.
- Provide concluding page numbers for all journal references and specific page numbers for all book references. Indicate all abstracts by the abbreviation (abstr).
- Follow the general arrangement, abbreviations and punctuation styles shown below.

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Examples of Styles of References

For periodicals, follow INDEX MEDICUS, listing *all* authors (if there are 7 or more, list only 3 and add et al.):

31. Vismara LA, Vera Z, Miller RR, Mason DT. Efficacy of disopyramide phosphate in the treatment of refractory ventricular tachycardia. Am J Cardiol 1977; 39:1027–34.

(Author: please note that no periods are used after authors initials)

For chapter in book:

28. Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. Heart Disease in Infants. Children and Adolescents. Baltimore: Williams & Wilkins, 1968:134–9.

For books (personal author or authors):

36. Berne E. Principles of Group Treatment. New York: Oxford University Press, 1966:26.

(Author: all book references should have specific page numbers.)

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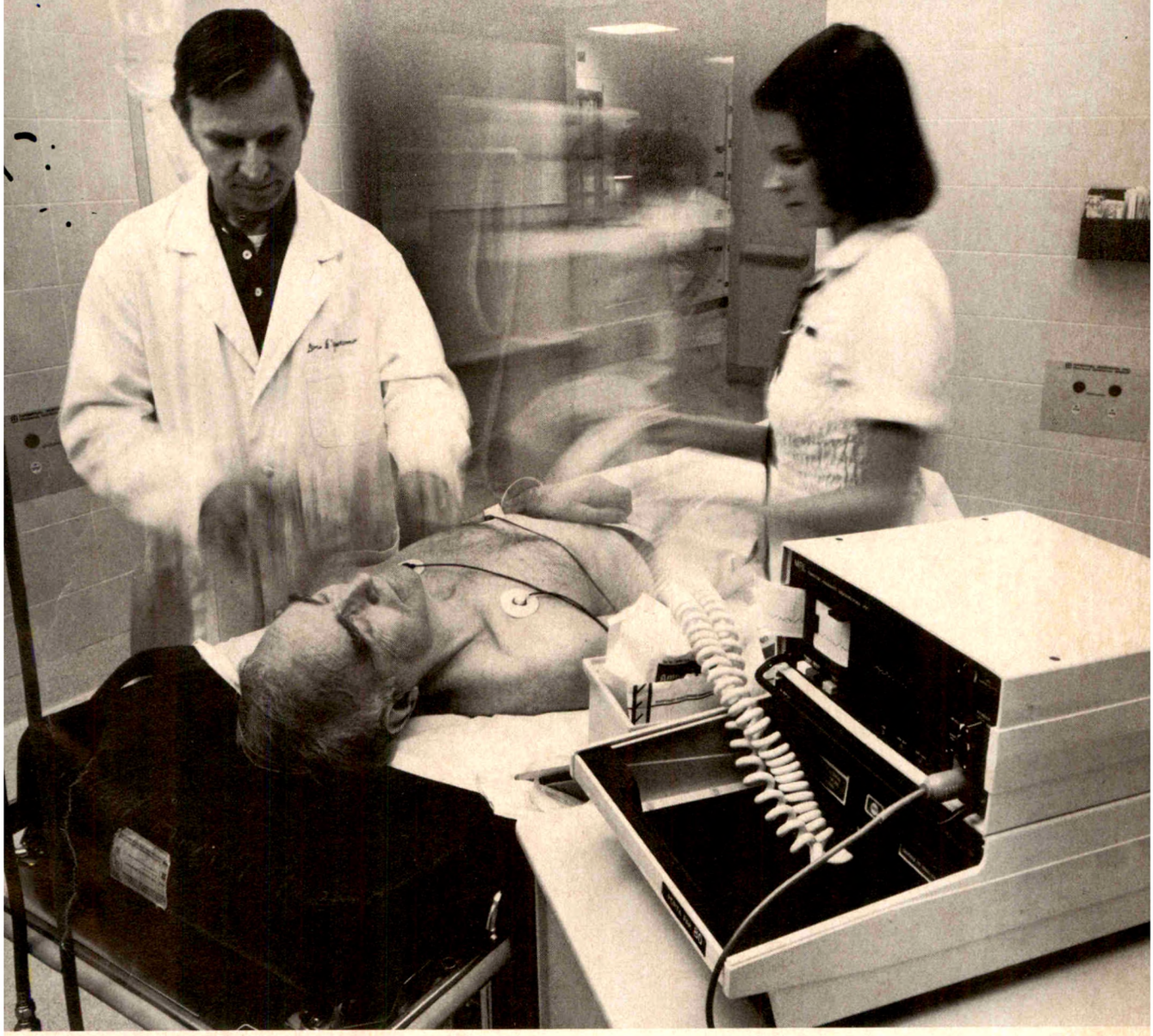

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MRL

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February 11, 1981

1,297,500 Shares

Intermedics, Inc.

Common Stock

Price $23 Per Share

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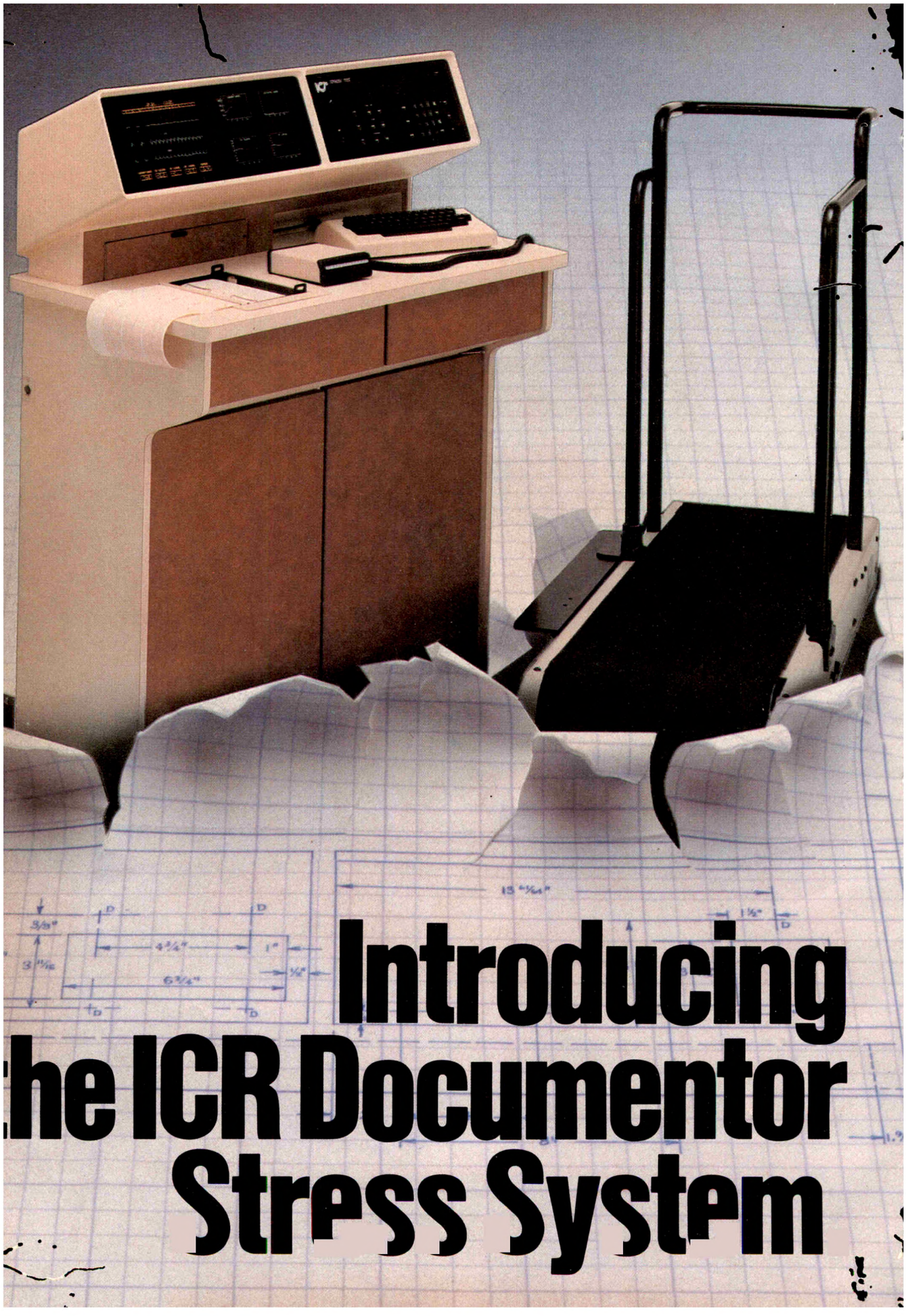

Introducing the ICR Documentor Stress System

See the new ICR Stress Systems at the A.C.C. Convention in San Francisco, March 16 to 19, Booth 1143.

4 Powerful advances in stress system capabilities from the leader in Holter technology.

Ten minutes of stress testing could be the key to your patient's life. Now, a breakthrough in stress technology from ICR enables you to find out more from those ten minutes than ever before possible.
Here's how.

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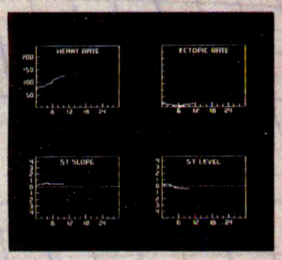

With the ICR Documentor, you can get more perspectives on your patient's condition faster and more easily with a comprehensive selection of display data. One display presents up to four trends simultaneously. The other display shows (and freezes) your choice of one to twelve continuous ECG wave forms, plus numerical data and averaged wave configurations.

2 Meaningful report information in your selection of formats.

The ICR Documentor lets you select the information and report format most meaningful to your diagnosis. Its unique microprocessor design gives it enormous power in generating a wide variety of information, and unsurpassed flexibility of report formats.

3 Complete programming from pre-exercise to report.

The ICR Documentor is the first stress system to give you complete programming ability over every phase of the test, including: pre-test procedures, treadmill protocol, recovery procedures, and display and report information. The Documentor saves time and paperwork and allows you to concentrate on the more critical aspects of the test.

4 Three-button operation simplicity.

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In addition to the Documentor, ICR is also introducing the Analyzer and Monitor. One of these systems is ideal for your practice, clinic or hospital. Each system can be upgraded quickly and easily in the field.
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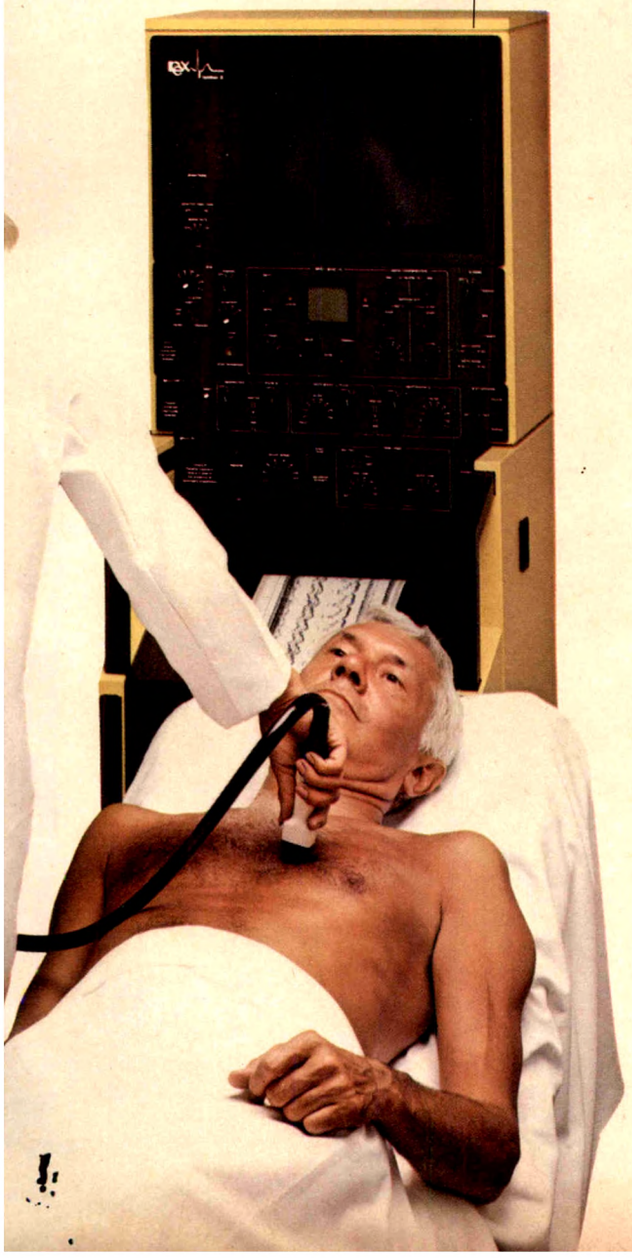

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ADVANCES AND NEW CONTROVERSIES 1981

This course will concentrate on important aspects of new advances and also upon new approaches to, and assessments of, old problems such as digitalis in sinus rhythm, the treatment of heart failure, pulmonary embolism, and anticoagulants in rheumatic heart disease. Pacemaking, electrophysiology, techniques of investigating myocardial ischaemia, echocardiography, calcium blocking agents, platelet agents and prostacyclins will be explored. Cardiac surgical topics, including circulatory assist devices, cardiac transplantation, long-term cardiopulmonary bypass, and valve replacement will also be considered.

A new feature will be introduced:—that of lunch-time sessions for small groups of participants who will discuss current problems in 'Meet the Experts' sessions and also have the opportunity to discuss the practical aspects of techniques of diagnosis and treatment in sessions on 'Practical Aspects of Investigation and Therapeutic Techniques'. In this way it is intended to increase the content of the course and also the contact between the participants and the lecturers.

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5 How to study arrhythmia by new electrophysiological approaches
6 How to evaluate total and regional myocardial perfusion and metabolism in man using computerised positron and single photon tomography in coronary artery disease and cardiomyopathy

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1 New diagnostic approaches to the diagnosis of angina
2 New therapeutic approaches to angina
3 Acute myocardial infarction: a new approach in prospect
4 Classification and evaluation of cardiomyopathies
5 Recent advances in treatment of cardiomyopathies
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8 Status of valve replacement today
9 Indications for surgery in coronary heart disease

Speakers include: J F Goodwin, A Maseri, H H Bentall, C M Oakley, D M Krikler, D Melrose, R N Sapsford and P Bourdillon (Royal Postgraduate Medical School) and experts from other international centres

Fee: (including catering) £75 for home students and member countries of the EEC £300 for overseas students

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ıtermedics Pulse Generators

DICATIONS AND CONTRAINDICATIONS

The indications for cardiac pacing are increasing as pacemakers come more sophisticated and as advanced methods for patient nagement become more widespread. Generally accepted indications for long-term cardiac pacing include, but are not limited to: sick sinus syndrome; (2) chronic, symptomatic drug-resistant us arrhythmias, including sinus bradycardia, sinus arrest, and sinoatrial (S-A) block as seen in sick sinus syndrome; (3) chronic, symptomatic second-degree or third-degree A-V block; (4) recurrent Adams-Stokes syndrome; (5) bradycardia-tachycardia syndrome; (6) symptomatic bilateral bundle branch block; and (7) hypersensitive carotid sinus syndrome (carotid sinus syncope). In addition, certain patients presenting such symptoms as intractable, recurrent congestive heart failure; cerebral or renal insufficiency; or recurrent, drug-resistant tachyarrhythmias, and who have been shown to benefit from temporary cardiac pacing, are considered candidates for permanent cardiac pacing.

The indications for permanent pacing in the presence of acut myocardial infarction have not yet been rigorously defined. Fac to be considered include the location of the myocardial infarct, presence or absence of symptoms, ventricular rate, the mechan of the arrhythmias, and response to therapy. In general, sympto matic drug-resistant bradyarrhythmias which impair cardiac out are considered indications for pacing in patients with acute myo cardial infarction, regardless of infarct location.

A CyberLith® pacemaker put Cedric Turgeon back in the saddle.

TIMELY HEART SURGERY, AND A CYBERLITH® PACEMAKER, RESTORED THE YOUTHFUL VIGOR OF THIS YOUNG VICTIM OF A CONGENITAL CARDIAC DEFECT.

Jumping, running, playing, riding...all are normal, everyday pursuits of a typical pre-schooler. But Cedric Turgeon, at three, tired too easily, and ran out of breath too quickly. His symptoms became acute one day, and his parents rushed Cedric from his home in Tampa, Florida, to the hospital.

Doctors performed a cardiac catheterization to reveal the extent of the youngster's heart defects. Surgery was performed, at which time temporary cardiac pacing was required. Ten days later, a permanent pacemaker—a CyberLith—was implanted.

Now 4½ years old, Cedric is back to his old tricks, with one exception: his energetic momentum is unabated. His friends find Cedric as competitive as the best of them.

And Cedric needn't suffer a routine of frequent trips to the hospital, because Cedric's doctor monitors the pacemaker telephonically.

If changes are required, Cedric's physician can change pacing parameters noninvasively.

Cedric's CyberLith is just one model in the growing family of specialized Intermedics CyberLith pacemakers. These thin, lightweight units permit noninvasive programming of stimulation rate, pulse width, sensitivity level and pacing mode. And CyberLith's history of reliability is longer than any other multi-programmable pacemaker line.

CyberLith put Cedric back in the saddle. It could be the pacemaker of choice for your patients.

Location of some photos courtesy of The Dark Continent, Busch Gardens, Tampa, Florida.

There are no known contraindications to the use of pacemakers as a medical method for control of heart rate. However, body rejection phenomena such as local tissue reaction or skin necrosis, muscle and nerve stimulation, embolism, and cardiac tamponade have been reported.

CAUTION: Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

Intermedics Inc.
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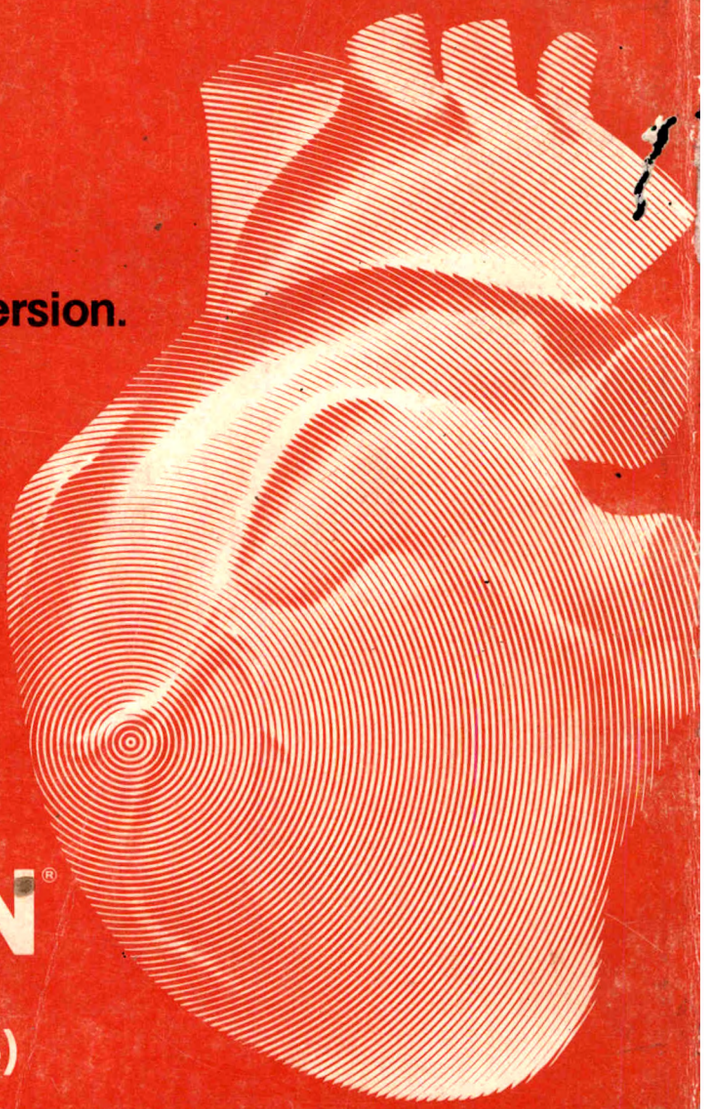
The Pacekeeper™

For ventricular arrhythmias.
For atrial arrhythmias.
For smooth, trouble-free conversion.
For steady maintenance.



CARDIOQUIN®
TABLETS
(quinidine polygalacturonate)

- ☐ Greater GI tolerance than with quinidine sulfate
- ☐ Full quinidine cardiodynamics
- ☐ Convenient b.i.d. or t.i.d. dosage for most patients

CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of a broad range of cardiac arrhythmias (see Brief Summary). After conversion to normal sinus rhythm—whether with CARDIOQUIN Tablets or electroconversion—only low b.i.d. or t.i.d. dosage of this unique polygalacturonate salt of quinidine is required for maintenance in most cases. The polygalacturonic acid serves as a buffering moiety. It protects the mucosa of the stomach and permits dependable absorption of the quinidine.*

*Aviado, D. M., Krantz and Carr's Pharmacologic Principles of Medical Practice, ed. 8, Baltimore, Williams and Wilkins Co., 1972, p. 456.

BRIEF SUMMARY—INDICATIONS: CARDIOQUIN Tablets (quinidine polygalacturonate) are indicated in the treatment of: premature atrial and ventricular contractions; paroxysmal atrial tachycardia; paroxysmal AV junctional rhythm; atrial flutter; paroxysmal atrial fibrillation; established atrial fibrillation when therapy is appropriate; paroxysmal ventricular tachycardia when not associated with complete heart-block; maintenance therapy after electrical conversion of atrial fibrillation and/or flutter. CONTRAINDICATIONS: Aberrant impulses and abnormal rhythms due to escape mechanisms should not be treated with quinidine. WARNING: In the treatment of atrial flutter reversion to sinus rhythm may be preceded by a progressive reduction in the degree of AV block to a 1:1 ratio and resulting extremely rapid ventricular rate. COMPOSITION: Each CARDIOQUIN Tablet (quinidine polygalacturonate 275 mg.) is equivalent in quinidine content to 3 grains quinidine sulfate. DOSAGE AND ADMINISTRATION: Dosage must be adjusted to individual needs, both for conversion and maintenance. An initial dose of 1 to 3 tablets may be used to terminate arrhythmias, and may be repeated in 3-4 hours. If normal sinus rhythm is not restored after 3 or 4 equal doses, the dose may be increased by ½ to 1 tablet (137.5 to 275 mg.) and administered three to four times before any further dosage increase. For maintenance, one tablet may be used two to three times a day; generally one tablet morning and night will be adequate. SUPPLIED: Uncoated, scored tablets in bottles of 100.

Purdue Frederick

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